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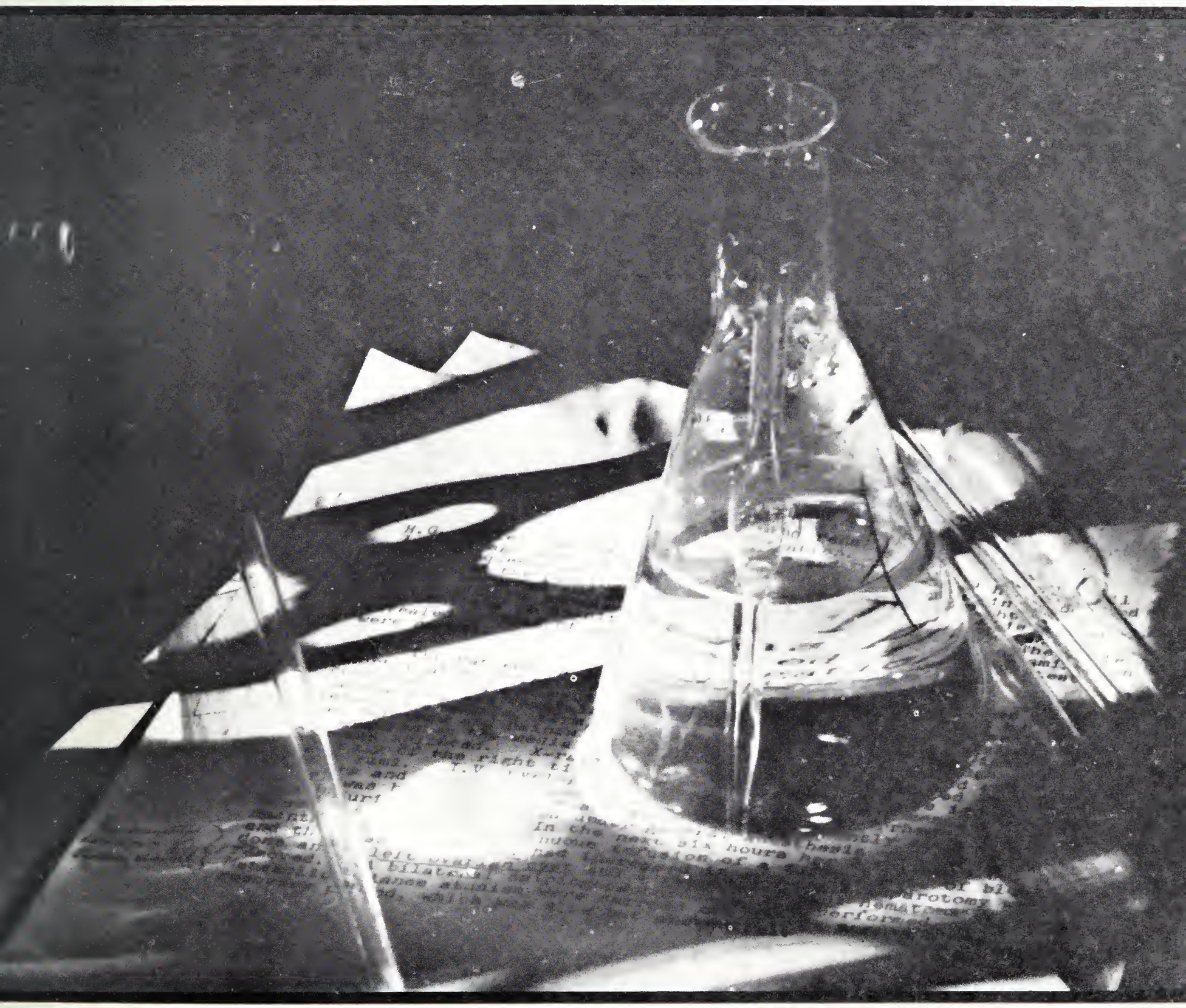

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VOLUME XL
NUMBER 1
NOVEMBER 1962

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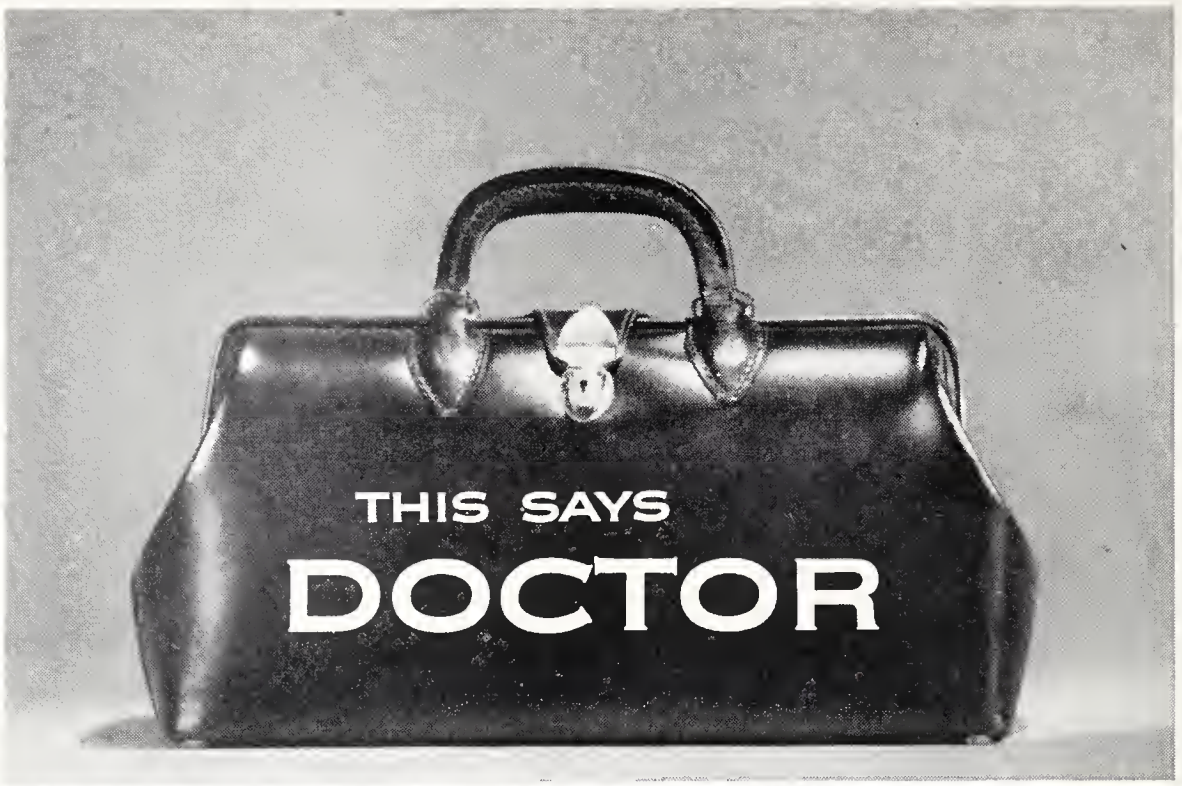
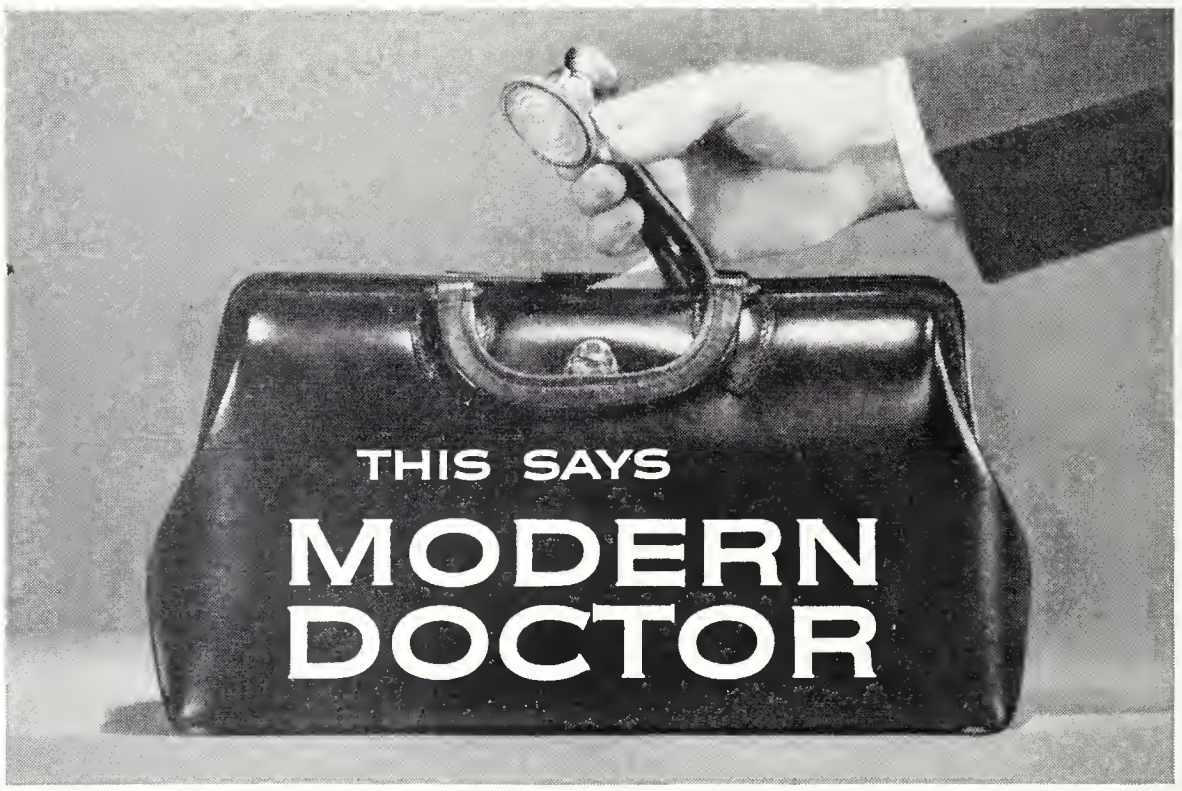
THE COVER

Shown on this month's cover are a few of the tools that a researcher might use. Some readers may see them as symbols: these readers may also attribute special significance to the black background and the ray of light focused on the paper. We prefer to let the photograph speak for itself, and introduce this Student Research issue.

D.P.A.





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Volume XL
Number 1
November 1962

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This Journal is published six times a year from November to April, by the Medical Society of the University of Toronto, to serve primarily as a medium for student expression.

Subscription rates: $4.50 for one volume of six consecutive issues. Single copies, $1.00.

Manuscripts including references and footnotes should be typewritten double spaced on one side of the paper. Articles should not exceed 3,000 words. Canadian Press (American) spelling is to be used. References should be kept to a minimum, and should be cited numerically in order in which they appear in the text.

Illustrations are included by arrangement with the Editor. Drawings should be done on white paper in black ink.

Final Copy Date is the 15th two months prior to issue. Mailing date is the 15th of the month of issue.

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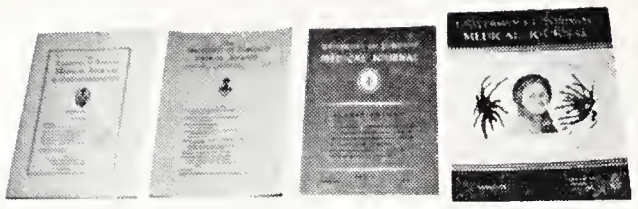
Correspondence should be addressed to

Room 114,
Medical Building,
University of Toronto,
Toronto 5, Canada.

Authorized as second class mail by the Post Office Department, Ottawa, and for payment of postage in cash.
Printers: General Printers, Oshawa, Ontario.

Editorials



THE FIRST FORTY YEARS

Pictured here are representatives of four eras in the publishing history of the University of Toronto Medical Journal. On the left is North America's first student medical journal, published in 1923. Second from the right is a red-covered Journal which Toronto's more recent graduates and senior students will remember. The right hand book is the latest member of the family.

Since its inception, the Journal has played an important part in a medical student's education. It has served as a medium for expression on medical topics, and has helped prepare many for the writing of post graduate articles. In addition, it has been a source of up-to-date review articles for students and graduates alike. Volume forty will follow its predecessors in these respects.

Regular features, not seen in the early issues, have become an important part of the Journal. In addition to the very popular *On Inspection, Recent Advances* has been retained as a regular feature in volume forty. *Medical Horizons,* a new feature, will be a vision (through the eyes of medical students) of medicine as it is practised in other countries. Another new feature, *Profiles,* will give short biographies of some prominent medical people in Toronto.

The mainstay of all of the thirty-nine previous volumes of the Journal has been the articles produced for them. Thirty-nine editors have spent countless man-hours striving to present the finest articles possible. This year, topics for each issue have been chosen to appeal to a wide range of interests: December—*Blood,* January—*General Practice,* February—*Mental Health* and March—*Clinical Nutrition.* As in the past, it is up to the student to break his personal barriers of dysphasia. To write for a journal is a tedious and sometimes unrewarding task. However, added stimuli are being provided in the form of cash writing prizes. Three Parke-Davis Prizes will be presented: one to a member of 4th year, another to a member of 3rd year and a third to a student in any other year of the faculty. To the best of these will go the Academy of Medicine's annual Webster Prize.

I leave you with a final thought: for forty years, articles have been written and submitted for publication with the knowledge that the *effort* of writing has as much or more value than the publication of the finished work.

J.D.G.

THIS ISSUE

It has been somewhat of a tradition in past years for medical students to engage in research projects in various basic science and medical departments of this university and other centres during the summer months. A number of these students have been asked to report on some aspect of their work.

Because the curriculum in medical school is so extensive, there is little time left for students to appreciate how experiments are designed to uncover scientific facts, and whether the data obtained is reliable and valid. However, when given an original problem to tackle in the laboratory, a student has time to think about all its facets in a more profound manner than is possible when he is occupied with school work. In addition, he is given the opportunity of learning and using some of the techniques which are employed in his particular field of enquiry. Last but not least, he has the privilege of associating with a full-time research scientist or clinician engaged in research.

The students contributing to this issue spent a summer or more working in several different fields. Mr. Sadowski worked for three summers in the Department of Pharmacology under Dr. W. Kalow. Mr. Hamer's work was conducted in the Department of Experimental Surgery under Dr. N. T. McPhedran. Mr. Growe and his associates performed their studies of hormones in the

Department of Medicine under Dr. C. Ezrin. The impetus for the article by Mr. Mintz and Mr. Norwich came from their work in the Department of Physiology under Drs. Hetenye and Wrenshall respectively. Mr. Weiser performed his intricate studies on blood vessel pathology under Dr. H. Movat in the Department of Pathology. Regeneration of nervous tissue was studied by Mr. Ball, working in the Department of Neuropathology under Dr. J. Olziewski.

R.B.

A CHALLENGE

"Those who do not remember the past are condemned to relive it." This incisive comment made by Santayana points to the fundamental importance of education in maintaining and advancing the fabric of our society. Its validity will exist for countless decades, creating an awareness of the need for knowledge in innumerable barren and semi-fertile minds.

With the rapid advance in technological skills and the mass media during the past quarter century, the demands on the human social animal are both overwhelming and frightening, so much so, that the commonest reaction pattern is that of withdrawal into anonymity, through mass conformity. This pattern holds a major threat to our social preservation.

A brief look at the present bibliography of social and political analysis reveals the concern that contemporary critics have for present day socio-political patterns. Titles such as *The Revolt of the Masses, The New Society, The Lonely Crowd,* well illustrate this trend of thought.

What then shall be our role, both as medical undergraduates, and as members of a wider academic community? Clearly it is to recognize the warnings of such sages as Santayana, and to avail ourselves of the opportunities of preparing, not only to be adept in our professional capacities, but also to be mature and facile in the sphere of national and international citizenship.

Here is the challenge: that you the undergraduates of this faculty, join the ranks of the minority of the "independents", and educate yourselves to perceive, digest, and appraise the complex parameters of our society, before accepting them as literal truths. E. H. Carr says, "Survival of western society appears to depend on the long term ability of the individual to reassert his independence of judgement, and on the vindication of reason against the irrational tendencies of our time."

R. H. Galway
President of the Medical Society

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Inborn Errors of Metabolism: Hypophosphatasia

Paul Sadowski 6T3

The author sketches the general biochemistry and treatment for all inborn errors of metabolism and goes on to discuss hypophosphatasia and his own research project.

INBORN ERRORS OF METABOLISM

Introduction

Over fifty years have passed since Garrod published his classic papers discussing the metabolic defects in alcaptonuria, cystinuria, albinism and pentosuria[1]. These four conditions formed the original "inborn errors of metabolism". Garrod regarded them as diseases of lifelong duration which resulted from the diminution of activity or complete absence of an enzyme catalysing a discrete metabolic step. Thus alcaptonuria was correctly attributed to the accumulation of homogentisic acid because of the absence of an enzyme necessary for its removal; albinism to the failure of melanin formation; and pentosuria to the inability to metabolise pentose. Garrod attributed cystinuria to a failure to oxidize cystine to sulphate. This view has required modification for it is now known that cystinuria results from the failure of the renal tubules to reabsorb cystine[2].

Definition

Dent[3] offers the following definition of an inborn error of metabolism. "By an inborn error of metabolism is meant a permanent inherited condition due to a primary enzyme abnormality. As a result, one or more chemical compounds may follow an altered metabolic pathway and may be found in some body fluids in greatly increased or decreased quantities."

Since Garrod's original publications, the number of diseases included under the title of inborn errors of metabolism has increased greatly. The most recent and exhaustive treatment of this field is the book entitled "The Metabolic Basis of Inherited Disease," edited by Stanbury, Wyngaarden and Fredrickson[4]. These authors have included forty-four disease entities in their work. In many of these diseases (for example diabetes mellitus and gout) the fundamental enzymatic aberration remains unknown. However the authors confidently believe that future discoveries will justify the inclusion of such diseases under the title of inborn errors of metabolism. Table 1 shows the conditions for which the enzyme defects have been demonstrated.

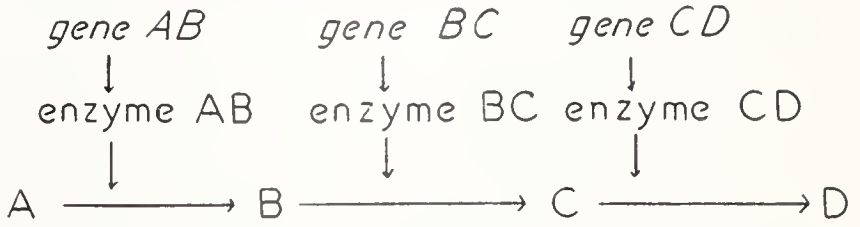
One Gene — One Enzyme Hypothesis

Implicit in the concept of inborn errors of metabolism is the "one gene — one enzyme hypothesis", first enunciated by Beadle[6]. This hypothesis includes the following tenets[7]:

1. All biochemical processes are under genic control.
2. These biochemical processes are resolvable into a series of individual stepwise reactions.
3. Each biochemical reaction is under the ultimate control of a different gene.
4. Mutation of a single gene results only in an alteration in the ability of the cell to carry out a single primary chemical reaction.

Consequences of a Metabolic Block

With the tenets of this hypothesis in mind, let us examine the various metabolic derangements that may occur. (After Stanbury et al.[4]). Let us represent the metabolic sequence A → D by the diagram shown below. Each gene controls a particular enzyme which in turn governs the rate of a particular reaction.



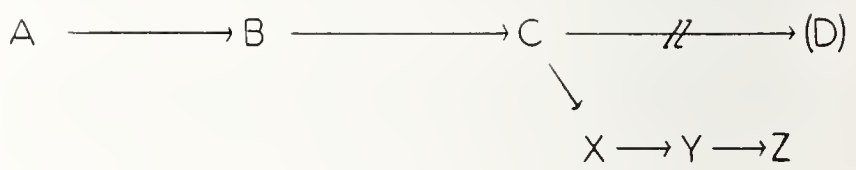
If gene *CD*, controlling the enzyme CD, is defective, then the reaction C → D is blocked. This block may result in the following disturbances.

1. *Failure to form adequate amounts of D or some product remote from D.* For example, the deficiency of typrosinase in albinism results in a failure to form melanin.

Condition	Deficient Enzyme	Tissue
Phenylketonuria	Phenylalanine hydroxylase	Liver
Alcaptonuria	Homogentisate oxidase	Liver, kidney
Galactosemia	Galactose—1—phosphate uridyl transferase	Red blood cells, liver
Hypophosphatasia	Alkaline phosphatase	Serum, white blood cells, bone, liver, kidney, intestine
Albinism	Tyrosinase	Skin
Glycogen storage Disease — A	Glucose—6—phosphatase	Liver, kidney
— B	Brancher enzyme	Liver
— C	Debrancher enzyme	Liver
— D	Muscle phosphorylase	Skeletal Muscle
— E	Liver phosphorylase	Liver
Congenital hyperbilirubinemia	Bilirubin glucuronyl transferase	Liver, kidney
Primaquine sensitivity	Glucose—6—phosphate dehydrogenase	Red blood cells
Acatalasia	Catalase	Serum, liver, bone marrow, muscle
Prolonged action of succinylcholine	Atypical cholinesterase	Serum

Table 1. Conditions for which an enzyme deficiency has been demonstrated (modified after Kretchmer et al.[5])

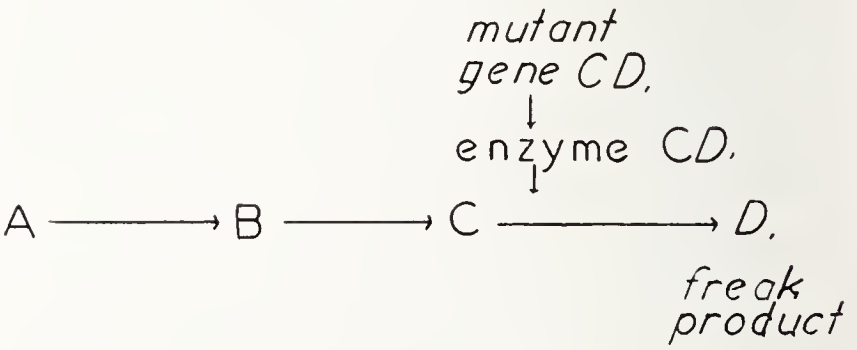
2. *Accumulation of C, the immediate precursor of D.* In alcaptonuria, homogentisic acid accumulates due to the absence of the enzyme homogentisate oxidase.



3. *Accumulation of A, a remote precursor of D.* This accumulation occurs through freely reversible reactions or via alternate pathways leading to the formation of A. In von Gierke's disease caused by glucose-6-phosphatase deficiency, blood lactate is elevated and hepatic glycogen is increased. Both substances are far removed from glucose-6-phosphate, the substrate of the deficient enzyme.

4. *Excessive production of products (X, Y, Z) normally produced in small quantities.* In phenylketonuria, the deficiency of phenylalanine hydroxylase results in the accumulation of phenylalanine. This in turn leads to the excessive production of phenylketones which are responsible for the observed clinical features of the disease.

5. *Production of a freak product by an abnormal enzyme.* Theoretically a structurally altered enzyme could result in the formation of structurally altered end products. For example, it is presumed that the structural abnormality in Sickle Cell Hemoglobin is conditioned by an abnormal enzyme which is in turn governed by a mutant gene.



Treatment

A rational form of treatment depends on an understanding of the fundamental disturbance in metabolism. The following therapeutic possibilities exist

1. *Limiting the intake of precursors which may accumulate in toxic quantities.* Good results have been achieved by limiting the intake of phenylalanine in

children with phenylketonuria. Children with galactosemia are benefitted by lactose-free diets.

2. *Supplying missing metabolites.* Thyroxine, if administered sufficiently early, may improve metabolic cretinism. Cortisone given to children with the adrenogenital syndrome results in amelioration of symptoms.

3. *Environmental control.* Avoidance of conditions known to cause symptoms of inborn metabolic errors is necessary. Thus a patient with red cells deficient in glucose-6-phosphate dehydrogenase should avoid taking primaquine and many other drugs. Barbiturates should be avoided by patients with porphyria.

4. *Depletion of stored substances.* Penicillamine is now used to deplete excessive copper stored in the tissues of patients with Wilson's disease. Venesection is used to deplete tissues of excessive iron in cases of hemochromatosis. Uricosuric agents are used to increase the urinary excretion of uric acid in patients with gout.

5. *Alteration of the underlying defect.* This would be the logical way to treat an error of metabolism but such treatment is at present not available.

Importance of Inborn Errors of Metabolism

The medical significance of an inborn error of metabolism, no matter how rarely it occurs, should not be underestimated. In pursuit of an explanation of the metabolic defect, the investigator inevitably uncovers information which clarifies physiological as well as pathological metabolism. Furthermore, this field contains material that interests virtually every scientific and clinical specialty in the field of medicine. For example, the disease hypophosphatasia has attracted the attention of biochemists, physiologists, pharmacologists, pathologists, geneticists, pediatricians, internists, orthopedic surgeons and neurosurgeons. Dent[3] believes that all hereditary diseases, even those which manifest themselves by grossly abnormal physical characteristics (e.g., achondroplasia), will ultimately be explained on the basis of a metabolic defect.

HYPOPHOSPHATASIA

Introduction

In 1948, Rathbun[8] described a hitherto unrecognised developmental anomaly. The patient was a three-week-old male with defective mineralization of bone, an elevated level of total calcium in serum and greatly reduced activity of serum alkaline phosphatase. After the death of the patient, the alkaline phosphatase activity of various tissues was found to be markedly diminished. Rathbun named the condition hypophosphatasia.

By 1957, Fraser[9] was able to collect from the literature thirty-five cases of what he considered to be typical examples of the syndrome. Affected patients were found to excrete phosphoethanolamine in their urine[10,11]. The hereditary nature of the disease has been established[9,12,13], although the mode of inheritance is still uncertain[14]. The fundamental metabolic disturbance in hypophosphatasia remains unexplained. This syndrome is decidedly uncommon. Fraser[9] has estimated the incidence in the Toronto area to be 1:100,000 live births. In Fraser's series of thirty-five cases, twenty-one were female and fourteen were male.

Age of Onset

Patients with hypophosphatasia have been divided arbitrarily into three groups according to the age of onset of the bony lesions. Group I includes those infants in which lesions are present at birth or appear within the first six months of life. Group II consists of children in whom lesions become evident after six months of age. Group III consists of patients in whom hypophosphatasia is first diagnosed in adult life.

In group I, general symptoms are prominent and bone lesions are severe. Systemic symptoms are uncommon in group II, and the prime complaint is usually of orthopedic deformities. There is no disturbance in general well being in group III. Patients usually present with delayed healing of a fracture or excessive fragility of bones.

Biochemical Findings

Serum Alkaline Phosphatase Activity. One of the cardinal findings in hypophosphatasia is a low value for the activity of alkaline phosphatase of serum. Taking into account the various methods used, Fraser estimated that the alkaline phosphatase activity of serum was reduced to less than 25% of the lower limit of normal.

The cause of this diminution of activity of alkaline phosphatase in serum remains to be elucidated. Inhibitors of alkaline phosphatase have been sought in the serum of patients with hypophosphatasia, but none has been found[11,16,17]. Magnesium, an activator of alkaline phosphatase, is present in normal concentrations in serum of patients with hypophosphatasia[9].

Two other possible interpretations of the diminished alkaline phosphatase activity exist. First, quantitatively less alkaline phosphatase may be circulating in the plasma. Second, it may be that due to some structural abnormality of the phosphatase, the reactions catalysed by this enzyme proceed at an unusually slow rate.

Korner[18] has attempted to demonstrate a structural

abnormality in the alkaline phosphatase of the serum from a patient with hypophosphatasia. He examined the pattern of distribution of alkaline phosphatase following the electrophoresis of serum on cellulose acetate strips. No deviation from the pattern observed in normal sera was observed.

The investigations described below attempted to demonstrate a structural abnormality in the alkaline phosphatase of serum in hypophosphatasia.

Tissue Alkaline Phosphatase. The activity of alkaline phosphatase in bone has been found to be reduced[10]. Likewise the activity of alkaline phosphatase of liver, kidney, spleen, lung and gastrointestinal mucosa of affected patients is diminished [8,10,16,19,20]. The activity of alkaline phosphatase in leukocytes is deficient[5]. Contrary to the findings noted above, Scaglione and Lucey[21] found that the activity of alkaline phosphatase of the liver and duodenal juice of an affected patient was normal.

Serum Calcium. Hypercalcemia is common in severely affected infants of Group I. In some cases the elevation of serum calcium is slight but in many, the serum calcium exceeds 14 mg %. Hypercalcemia is uncommon in children of Group II and in adults.

Patients with hypercalcemia are in positive calcium balance. There is no evidence of excessive resorption of bone, nor is there any urinary retention of calcium. Hence Fraser[9] concludes that calcium is absorbed from the intestine faster than it can be deposited in the skeleton.

Serum Phosphorus. Serum phosphorus determinations are within the normal range.

Renal Function. Nitrogen retention, proteinuria and impaired ability to concentrate urine are evidence of renal damage in patients of Group I. Occasional cases in Group II have impaired renal function. Renal function is normal in adult cases. Renal damage is attributed to hypercalcemia.

Phosphoethanolaminuria. Two groups of investigators working independently, reported the isolation of an abnormal ninhydrin-reactive substance from the urine of patients affected with hypophosphatasia[10,11]. This substance was proved to be phosphoethanolamine[22,23]. Its chemical structure is shown in figure 1.

Since these reports have appeared this substance has also been isolated from the urine of patients suffering from scurvy[24], hypothyroidism[24] and celiac disease[25]. These conditions are characterized by abnormally low values of alkaline phosphatase activity in serum.

Because of the abnormal excretion of phosphoethanolamine in conditions accompanied by a low activity of alkaline phosphatase in serum it has been suggested that phosphoethanolamine is in fact the "physiologic substrate" for alkaline phosphatase[10,11]. When the activity of alkaline phosphatase is deficient, the unhydrolysed substrate escapes into the urine. Indeed, alkaline phosphatase is capable of hydrolysing phosphoethanolamine[17,26,27].

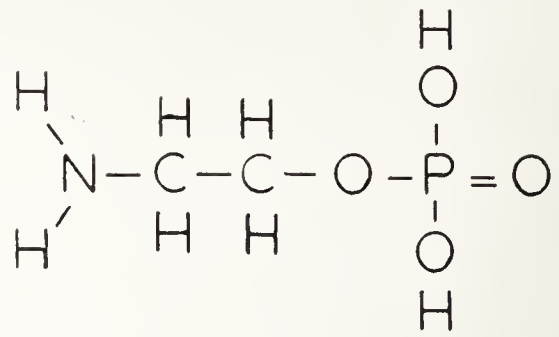


Fig. 1. The chemical structure of phosphoethanolamine, the proposed physiologic substrate for alkaline phosphatase.

Phosphoethanolamine is found in many tissues which include brain, liver, kidney, intestine, and pancreas[28]. One conspicuous omission from this list of tissues is bone, which does not seem to have been investigated.

Phosphoethanolamine does not inhibit the activity of alkaline phosphatase in serum using p-nitrophenylphosphophate as substrate[29]. If phosphoethanolamine were the physiologic substrate for alkaline phosphatase, one might expect that it would compete with an artificial substrate for access to the active centre on the alkaline phosphatase of serum. The study of McCance et al.[17] showed that a patient with hypophosphatasia had no disability to handle an injected load of phosphoethanolamine. This patient appeared to be able to hydrolyse phosphoethanolamine at a normal rate. Thus, though there is little direct evidence to implicate phosphoethanolamine as the natural substrate for alkaline phosphatase, there is no alternative explanation for the phosphoethanolaminuria observed in patients with hypophosphatasia, scurvy, celiac disease and hypothyroidism.

Inheritance

Hypophosphatasia is thought to be inherited as an autosomal recessive character. This means that an affected person has received one abnormal gene from each parent. The affected patient is said to be "homozygous" for the gene causing hypophosphatasia. Each of the patient's parents is a carrier of this abnormal gene and is said to be "heterozygous".

It was predicted that although carriers of hypophosphatasia were clinically normal, they might exhibit

some metabolic abnormality similar to those observed in affected patients. Two methods have been used to detect carriers of hypophosphatasia: the finding of a low level for the activity of alkaline phosphatase in serum, and the detection of excessive excretion of phosphoethanolamine in the urine.

About 70% of heterozygotes can be detected by using only the level of activity of alkaline phosphatase in serum as a criterion[9]. Harris and Robson[13] used the detection of phosphoethanolamine in the urine as a criterion of heterozygosity. These workers investigated 381 relatives of patients affected with hypophosphatasia. 81 of these excreted abnormally large amounts of phosphoethanolamine in their urine. Analysis of the relationship of these people to the patients affected with hypophosphatasia suggested that the disease is inherited as an autosomal recessive. 58% of the estimated number of heterozygotes could be detected using this method. Using both methods 81% of parents could be classified as carriers[9].

The expected incidence of the disease in the children of two carriers is 25%. The calculated frequency among siblings in Fraser's series was 26.4%[9] and in the series of Currarino et al. it was 28%[12].

Recently Silverman[14] reported a family in which the father and two children were proved clinically and chemically to have hypophosphatasia but the mother and four other siblings were entirely normal. This finding suggests that hypophosphatasia may be inherited as a dominant trait.

Pathogenesis

A discussion of the pathogenesis of hypophosphatasia necessitates a brief review of theories about the relationship of alkaline phosphatase to bone formation. Robison[30] suggested that alkaline phosphatase liberated inorganic phosphate at the site of calcification of bone and thus caused an increase in the Ca × P activity product. This rise initiated crystallization. Gutman and Yu[31] found that an inhibitor of glycolysis such as iodoacetate could inhibit calcification of cartilage even in the presence of adequate concentrations of calcium and phosphate. These authors proposed that alkaline phosphatase catalysed the transfer of phosphate ions from organic phosphate esters to receptor sites on the bone matrix. A third theory is that alkaline phosphatase functions in the formation of organic bone matrix [32,33,34]. Finally, Fleish and Neuman[35] have suggested that alkaline phosphatase functions to destroy an inhibitor of the calcification process. These authors have purified a substance from plasma which inhibits the calcification of collagen *in vitro*. This substance can be destroyed by alkaline phosphatase.

That alkaline phosphatase plays some important role in the formation of bone is shown dramatically by the condition hypophosphatasia. It has been hoped that a study of this condition would further clarify the mechanisms underlying bone formation. Fraser et al.[11] demonstrated that rachitic cartilage would calcify in the presence of serum from a patient with hypophosphatasia. However cartilage from the costochondral junction of a patient with hypophosphatasia would not calcify in the presence of normal serum[36]. It seems clear that the alkaline phosphatase circulating in serum serves no function in relation to bone formation. In hypophosphatasia the defect is localized to the cells which produce alkaline phosphatase, that is the proliferating osteoblasts and hypertrophic chondrocytes. The diminution of alkaline phosphatase activity of serum must be considered as a secondary phenomenon, reflecting a deficiency in production of the enzyme by bone (and perhaps liver, kidney and intestine).

The work of Scaglione and Lucey[21] suggests that the inability of the osteoblasts to produce adequate alkaline phosphatase is not under direct control of the gene that causes hypophosphatasia. These workers removed a piece of bone from the skull of a patient severely affected with hypophosphatasia. This bone contained no detectable alkaline phosphatase activity. A fragment of bone was placed on a tissue culture medium and a group of cells with characteristics like osteoblasts proliferated. These cells were rich in alkaline phosphatase. It was concluded that the tissue culture medium provided a more favorable environment for the production of alkaline phosphatase than did the internal environment of the original bone. Hence it is entirely possible that although the bone cells have the proper genetic equipment to make alkaline phosphatase, some factor, perhaps genetically determined, prevents adequate production of the enzyme.

Treatment and Prognosis

Many forms of treatment have been tried in hypophosphatasia. These have included Vitamin C, thyroid extract, testosterone, growth hormone, oral citrate and benemid. None of these preparations has affected the course of the disease.

Fraser and Laidlaw[37] have reported a favourable response of one patient to the administration of oral cortisone. Within ten weeks calcification of bones had improved, activity of alkaline phosphatase in serum had risen and serum calcium had fallen. When cortisone was withheld for two months, skeletal lesions reappeared and the activity of alkaline phosphatase of serum fell. Other workers have failed to find cortisone of benefit in the treatment of hypophosphatasia[38,39].

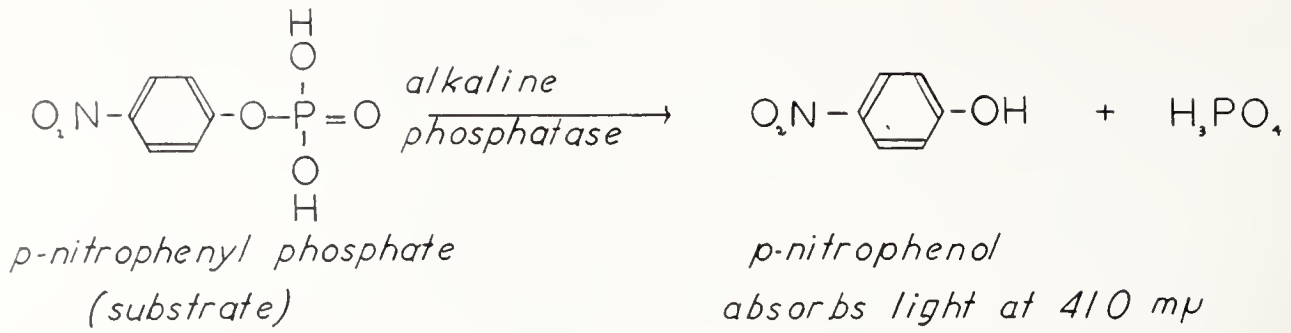


Fig. 2. The breakdown of p-nitrophenyl-phosphate by alkaline phosphatase.

As a general rule, the earlier is the onset of the disease, the more severe is the clinical picture and the poorer is the prognosis. In cases where the disease appears soon after birth, death within the first year of life is to be anticipated. If the infant survives the first year of life the condition usually improves. The life expectancy of the less severely affected children and of the adults is probably normal.

Original Investigations

In the present investigation an attempt was made to demonstrate a structural abnormality in the alkaline phosphatase of serum from patients with hypophosphatasia by investigating the kinetic properties of the enzyme in normal and pathological sera.

The Michaelis Constant (Km) is an expression of the dissociation of the enzyme-substrate complex. Hence the inverse of the Km is a measure of the affinity of the enzyme for its substrate.

The substrate used was p-nitrophenyl-phosphate. This substance is hydrolysed by alkaline phosphatase to p-nitrophenol and phosphoric acid (see figure 2). P-nitrophenol absorbs light at 410 mμ. The increase in optical density of the solution at 410 mμ is measured in a spectrophotometer, and is a measure of the velocity of reaction. The velocities were measured in the presence of variable concentrations of substrate.

The data were plotted in the 1/V:1/S plot of Lineweaver and Burk[10] and the Km values obtained graphically. The Km of the alkaline phosphatase in the serum of a patient affected with hypophosphatasia did not differ materially from the values obtained using normal sera. Hence it was concluded that a structural abnormality in the alkaline phosphatase in the serum of a patient with hypophosphatasia could not be demonstrated by measuring affinity constants.

In a further attempt to characterise the hypophosphatasic enzyme, the percent inhibition of alkaline phosphatase activity by β-naphthyl-phosphate was determined. β-naphthyl-phosphate competes with p-nitrophenylphosphate for access to the active centre on the enzyme. Normally the activity of alkaline phosphatase from serum was inhibited about 54% by a given concentration of β-naphthyl-phosphate. The alkaline phosphatase from sera of some hypophosphatasic children showed a significantly lower percent inhibition by β-naphthyl phosphate.

The nature of the structural abnormality indicated by this test is not clear. The test suggests that the alkaline phosphatase from a patient with hypophosphatasia binds β-naphthyl-phosphate less readily than the normal enzyme. The data obtained in this study were considered to show that perhaps further search for an enzyme alteration in hypophosphatasia may be rewarding.

ACKNOWLEDGEMENTS

I wish to thank Dr. Donald Fraser, Hospital for Sick Children, for supplying serum samples used in the investigation. Appreciation is expressed to Dr. Nancy Simpson, Department of Pharmacology, for advice about the section concerning inheritance. Sincerest thanks are due to Professor Werner Kalow, Department of Pharmacology, for his stimulating guidance during the course of the investigations and his criticisms of the paper.

REFERENCES

1. Garrod, A. E., Lancet 2:1, 73, 142, 214, 1908.
2. Dent, C. E., Senior, B., Walshe, J. M., J. Clin. Invest. 33: 1216, 1954.
3. Dent, C. E., Am. J. Med. 22:671, 1957.
4. Stanbury, J. B., Wyngaarden, J. B., Fredrickson, D. S. (editors), The Metabolic Basis of Inherited Disease, McGraw-Hill, 1960.
5. Kretchmer, N., Stone, M., Bauer, C., Ann. N.Y. Acad. Sci. 75(1):279-85, 1958.
6. Beadle, G. W., Chem. Rev. 37:15, 1945.
7. Tatum, E. L., Science 129:1711, 1959.
8. Rathbun, J. C., Am. J. Dis. Child. 75:822, 1948.
9. Fraser, D., Am. J. Med. 22:730, 1957.
10. McCance, R. A. Morrison, A. B., Dent, C. E., Lancet 1:131, 1955.
11. Fraser, D., Yendt, E. R., Christie, F. H. E., Lancet 1:286, 1955.
12. Currarino, G., Neuhauser, E. B. D., *et al.*, Am. J. Roentgen. 78:392, 1957.
13. Harris, H., Robson, E. B., Ann. Hum. Genet. 23:421, 1959.
14. Silverman, J. L., Arch. Int. Med. 110:191, 1962.
16. Engfeldt, B., Zetterstrom, R., J. Pediat. 45:125, 1954.
17. McCance, R. A., Fairweather, D. V. I., *et al.*, Quart. J. Med. 25:523, 1956.
18. Korner, N. H., J. Clin. Path. 15:200, 1962.

19. Sobel, E. H., Clark, L. C., *et al.*, Pediatrics 11:309, 1953.
20. Rosenthal, I. M., Bonting, S. L., Am. J. Dis. Child 99:185, 1960.
21. Scaglione, P. R., Lucey, J. F., Am. J. Dis. Child 92:493, 1956.
22. Fraser, D., Lucas, C. C., Can. J. Bioch. 35:1123, 1957.
23. Cusworth, D. C., Bioch. J. 68:262, 1958.
24. Fraser, D. Unpublished observations, quoted in Hypophospatasia, Fraser, D. (9), Am. J. Med. 22:730, 1957.
25. Lee, M., Lancet 1:334, 1955.
26. Strickland, K. P., Thompson, R. H. S., Webster, G. R., Arch. Boch. & Biophys. 64:498, 1956.
27. Smith, L. C., Rossi, F. M., Proc. Soc. Exp. Biol. Med. 99:757, 1958.
28. Astrup, T., Carlstrom, G., Stage, A., Acta Physiol. Scandinav. 24:202, 1951.
29. Sadowski, P. Unpublished observations, 1962.
30. Robison, R., Biochem. J. 17:286, 1923.
31. Gutman, A. B., Yu, T. F., Josiah Macy Jr. Foundation, Tr. Conf. Metabolic Interrelations 2:167, 1950.
32. McKelvie, A. M., Mann, F. C., Proc. Staff Meet. Mayo Clin. 23:449, 1948.
33. Siffert, R. S., J. Exp. Med. 93:415, 1951.
34. Glimcher, M. J., Hodge, A. J., Schmitt, F. O., Proc. Nat. Acad. Sci. U.S. 43:860, 1957.
35. Fleish, H., Neuman, W. F., Am. J. Physiol. 200:1296, 1961.
36. Fraser, D., Yendt, E. R., J. Dis. Child 90:552, 1955.
37. Fraser, D., Laidlaw, J. C., Lancet 1:553, 1956.
38. Dent, C. E., Personal communication 1957, cited by Fraser D. (9), Hypophosphatasia, Am. J. Med. 22:730, 1957.
39. Beisel, W. R., Austen, K. F., Rosen, H., Herndon, F. G., Jr., Am. J. Med. 29:369, 1960.
40. Lineweaver, H., Burk, D., J. Am. Chem. Soc. 56:658, 1934.

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Abstract –

Sudden Arterial Occlusion: a Clue to Silent Myocardial Infarct. Proc. of Mayo Clinic, Vol. 37, No. 11, May 1962.

An embolic arterial occlusion may be the only symptomatic manifestation of an acute myocardial infarction. The heart is the most common source of arterial emboli (90%); a small number of emboli have either an arterial aneurysm or an atherosclerotic plaque as their source. The patient's ECG is usually helpful. It is important to ascertain the origin of the embolus, for in the cardiac patient embolectomy is too great a risk. Conservative treatment employing anticoagulants and bed rest is preferred. *F.L.*

On Inspection

S. M. Zweig 6T3
D. P. Armitage 6T3

FIGURE 1: Name the type of dwarf. List the varieties of dwarfism with their distinguishing features. See also Fig. 4.

FIGURE 3: What common clinical condition does the above picture represent? List the causes. Name an endocrine disorder which might cause a similar picture to appear in only one finger.

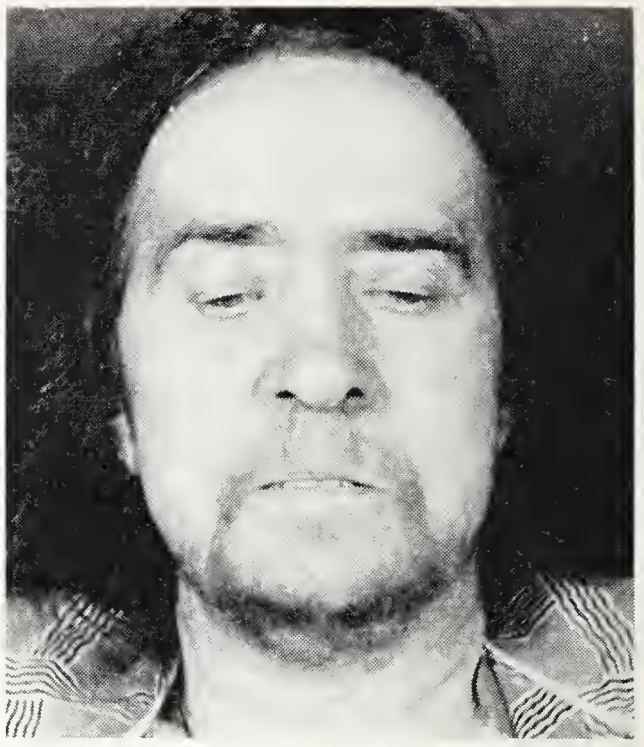

FIGURE 2: Urinary Ketosteroids — 800 mgm/day: What are some possible diagnoses?

FIGURE 4: Height: 51 inches. Of what condition is this a classical representation?

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FIGURE 5: Name the lesion pictured and the endocrine disease of which it is a part.

FIGURE 6: Patient presented with brownish-black pigmentation of tongue, palmar creases, and previous scars: diagnosis?

FIGURE 7: This patient underwent a thyroidectomy during which her parathyroid glands were inadvertently removed. Replacement therapy included large doses of vitamin D. She subsequently developed hard nodules in the above pictured areas. She also developed a chronic pyelonephritis. What is the diagnosis?

See page 43 for answers.

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Influence of the Islets of the Pancreas on Gastric Secretion

H. Hamer 6T3

Experiments with normal and abnormal pancreas are performed in an attempt to explain the physiology involved in the Zollinger-Ellison syndrome.

THE ZOLLINGER-ELLISON SYNDROME

In 1955 Zollinger and Ellison described a rare clinical entity of fulminating peptic ulceration associated with islet cell tumour of the pancreas. The syndrome then included (1) excessive gastric secretion with rapidly progressive atypically located peptic ulceration recurring despite adequate medical or surgical therapy, and (2) a non-insulin producing tumour of the islets of the pancreas. It is now apparent that these patients may also present with (3) chronic diarrhea without ulcer in some patients or preceding ulceration in the remainder of patients, and (4) a pancreatic tumour not typically alpha or beta islet cell in type.

Clinical Course. Patients with the Zollinger-Ellison syndrome most commonly present with ulcer or less often with diarrhoea. Patients have ranged in age from 19 to 78 years, and females are affected as often as males. The ulceration may be multiple and may frequently be atypically located, being either in the second or third part of the duodenum or in the proximal jejunum. These ulcers have a great tendency to perforate, and may recur rapidly following what is considered an adequate operation for the usual type of complicated peptic ulcer.

Laboratory Studies. In the majority of patients studied[2], overnight gastric secretion was greater than 1500 ccs. and total free HCL secretion exceeded 100 mEq. There was a relatively small difference between basal and histamine-stimulated gastric secretion, as if the stomach were already under maximal stimulation prior to histamine injection.

In the majority of patients with diarrhea, stool volume varied between 500 - 7900 ccs. for twenty-four hours, serum potassium values were low, and many had evidence of an abnormal carbohydrate metablolism, for example, a diabetic glucose tolerance curve.

Pathology. In 90% of patients with this syndrome, the tumours have been in the pancreas, but in 10%, the tumours have been located in aberrant pancreatic tissue. Two out of three of the pancreatic tumours have occurred in the body or tail. 37% of patients have had multiple tumours, while 37% have had at least one proven malignant islet adenoma.

Microscopically, the cells in these tumours were islet cell in type, being grouped into nests separated by broad bands of stroma and surrounded by capillaries. Special staining methods have failed to definitely identify these cells as either alpha or beta cells.

The Zollinger-Ellison syndrome is closely related to the disease known as polyglandular disorder (or multiple endocrine disease) because as many as 20% of patients with this syndrome have been shown to have multiple endocrine tumours.[3] As well as the tumour in the pancreas, these patients have had tumour(s) in at least one of the adrenal cortex, pituitary, or parathyroid.

Management. Medical management is unsatisfactory. Surgical management should include an extensive gastric resection along with removal of the tumour because of the high incidence of malignancy and the large number of patients with multiple tumour, either of which may render complete removal of the tumour impossible.

EXPERIMENTATION

Tumour Extracts

Gregory et al in England were the first to demonstrate a rise in secretion from vagally denervated gastric pouches (Heidenhain pouches) in dogs following injection of extracts of ulcerogenic tumour.[5] Their experimentation substantiated the view that a hormone secreted by the pancreatic tumour caused the dramatic rise in gastric secretion seen in the Zollinger-Ellison syndrome, and that the hormone acted directly on the gastric mucosa without the mediation of the vagus nerve.

In this laboratory, extracts of diarrhea-producing pancreatic tumour were tested in a series of prepared dogs. The duodenum was transected near the pylorus and the terminal ileum near the caecum. The pyloric

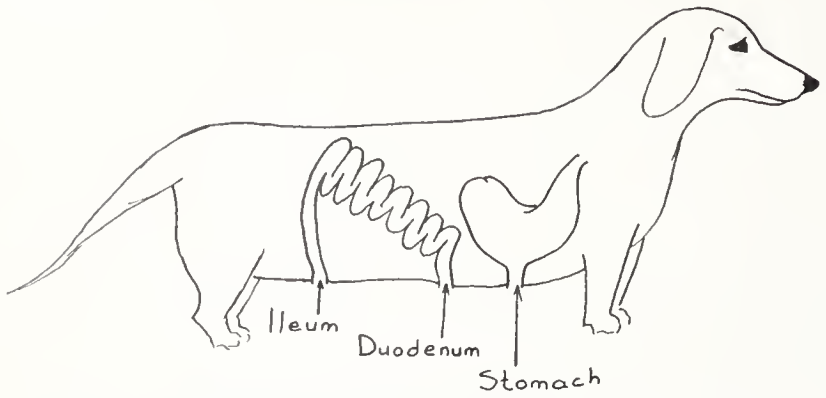

Figure 1. Dog prepared for testing with pancreatic tumour extracts.

end of the transected duodenum was exteriorized to isolate the stomach. The distal end of the transected duodenum and the proximal end of the terminal ileum were exteriorized separately to isolate the small bowel. (See figure 1) Stomach and small bowel contents were collected independently from fasting conscious dogs during basal conditions and following administration of extract.[5]

Saline extracts of a diarrhea-producing tumour produced marked gastric hypersecretion, but failed to stimulate intestinal secretion. The failure to stimulate directly small bowel secretion clarifies the mechanism of the diarrhea in this disease. It results probably from gastric hypersecretion "running through" or by hypersecretion secondarily stimulating intestinal secretion. Extracts of hepatic and lymph node metastases have also stimulated gastric secretion in other experimental series.[7,8]

Thus, both ulcer-producing and diarrhea-producing islet cell tumours have been shown to contain a gastric stimulating hormone, the identity of which remains to be established. It is not histamine, for all tumour extracts tested so far have contained too small a concentration of histamine to be potent. It is not glucagon, for glucagon decreases stomach motility and acid secretion, and does not produce diarrhea on human administration.[9] It is not insulin, for our patient with this tumour did not have hypoglycemia and our dogs did not develop hypoglycemia during administration of the extracts. It resembles most the hormone *gastrin*. Both gastrin and this hormone produce gastric hypersecretion and hyperacidity without affecting pepsin concentration.

Normal Pancreas Extracts

Since a "gastrin like" hormone had been shown to be produced in tumours of the pancreatic islets, it seemed possible that such a hormone might be found in the islets of the normal pancreas. Evidence for such a hormone is provided by the finding in dogs that diversion of pancreatic secretion from the duodenum (by duct ligation or by fistula) is followed by a high incidence of peptic ulcer. Total pancreatectomy however, is followed by a minimal incidence of peptic ulcer[10] and therefore the absence of external pancreatic secretion does not account for the occurrence of the ulcers. It is probable that an internal pancreatic secretion is involved.

To investigate this possibility, extracts of normal human and animal pancreas were prepared. These extracts were tested to determine whether they stimulated gastric secretion in a vagally denervated pouch and a vagally innervated pouch. The stomach of a series of dogs was divided along the greater curvature to create a vagally denervated (Heidenhain) pouch and its orifice was exteriorized. The duodenum was transected near the pylorus and the remainder of the stomach exteriorized to create a vagally innervated gastric fistula. A feeding tube was left in place in the distal duodenum.

At this writing, several encouraging results have been obtained after intravenous and subcutaneous injection of extracts of normal dog pancreas. An example is shown in figure 2. A two hour control period preceded injection. Thirty minutes after injection both gastric and pouch secretions rose, the response in the stomach lasting up to ninety minutes. Such a response curve resembles those reported for gastrin.

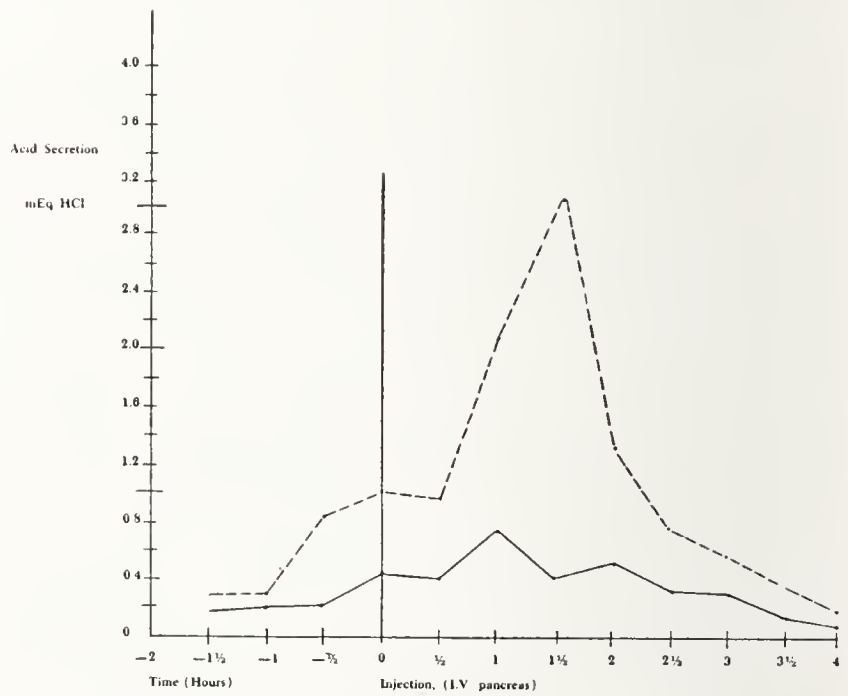

Figure 2. Dog #13, Extract of Normal Dog Pancreas, 10 cc. I.V.
Total acid, vagally innervated stomach – – –
Total acid, vagally denervated pouch ————

If such a response is repeatedly obtained, it may help substantiate the hypothesis that the normal pancreas produces and secretes a "gastrin-like" hormone.

It is attractive to entertain the possibility that a more highly concentrated extract of this hormone will be obtained in the future by producing atrophy of the exocrine part of the pancreas (ligating the ducts) and by destroying the beta cells with alloxan and the alpha cells with synthalin.[11]

Summary

A syndrome is described in which gastric hypersecretion caused by islet cell tumour of the pancreas leads to peptic ulcer or diarrhea. Extracts of these tumours injected in dogs produce gastric hypersecretion. The active hormone in the extracts is not insulin, glucagon, or histamine, but it does resemble gastrin. There may be a similar hormone in the normal pancreas, because extracts of normal dog pancreas have been shown to stimulate gastric secretion in some dogs.

ACKNOWLEDGEMENTS

I would like to thank Dr. R. Henderson and Dr. R. Mathews for their eritieism of this paper, and Dr. N. T. MePhedran for his guidance and inspiration in writing this paper, and throughout the summer months.

REFERENCES

1. Zollinger, R. M., and Ellison, E. H. Annals Surg., 142: 704, 1955.
2. Howard, J. M., and Jordan, G. L. Surgical Diseases of the Panereas, J. B. Lippineott Co., P. 443, 1960.
3. Proeeedings of the Staff Meetings of the Mayo Clinic, Nov. 22, 1961, 36, 24.
4. Zollinger, R. M. Gastroenterology, 39, 5, Nov. 1960..
5. Gregory, R. A., Traey, H. S., French, J. M., Sircus, W. Laneet, 1:1045, 1960.
6. Mathews, R. E., Bett, H. D., Edmeads, J. G., Ezrin, C., MePhedran, N. T. Surg. Obs. and Gyn. Nov. 1962 (not yet in print).
7. Grossman, M. I, Traey, H. J., Gregory, R. A. Gastroenterology, 41:87, 1961.
8. Freisen, S. R., Traey, H. S., Gregory, R. A. Annals Surg. 155:2, Feb. 1962.
9. Ezrin, C., Salter, J. M., O'Gryzlo, M. A., and Best, C. H. Can. M. A. J., 78:96, 1958.
10. Poth, E. S., Manhoff, L. S., and Delsach, A. W. Surgery, 24:62, 1948.
11. Ferner, H. Ciba Foundation Colloq on Endoe., 9:2-13, 1956.

Abstracts –

The Diabetic Charcot Joint. New England Journal of Medicine — Vol. 267, no. 4. July 26, 1962.

The Charcot joint can be defined as a painless flail joint, and occurs in six conditions: 1. Tabes dorsalis, 2. Syringomyelia, 3. Diabetes Mellitus, 4. Congenital absence of pain, 5. Leprosy, 6. Osteomyelitis.

A case is described of diabetic neuropathic arthropathy: A known diabetic (44 year old male) stumbles. This results in swelling and ecchymoses over the foot. Neurologically therc was a complete loss of pinprick sensation below the knee, fixed pupils, diabetic retinopathy, and loss of patellar and achilles reflexes bilaterally. Also, there was 2+ protein, and 4+ glucose in the urine. The roentgenologic findings were also significant: extensive osteolytic and hypertrophic changes were found, involving the proximal five metatarsals and adjacent tarsals, with destruction of respective joints. *F.L.*

Critical Evaluation of Massive Steroid Therapy of Acute Leukemia. New England Journal of Medicine, Vol. 266, no. 26, 28 June 1962.

Doses of prednisolone were employed — 50 to 500 mg. per day. Only patients with acute lymphocytic leukemia showed hematologic benefit with this therapy. The courses of either acute granulocytic monocytic, or plasma cell leukemia regardless of dosage, were unaffected. Massive doses of corticoids produced a more rapid remission than lesser doses but not a remission of greater duration. *F.L.*

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Chlorothiazide Studies

Jerry Growe 6T3
Allan Gross M.D. 6T2
John Ireton M.D. 6T2

The sometimes dramatic antidiuretic effect of chlorothiazide with diabetes insipidus has led the authors to investigate the drug's action in the kidneys of dogs — both normal and diabetic.

DIABETES INSIPIDUS

The elinical syndrome of polyuria and polydipsia further characterized by urine of a persistently low osmolarity is known as diabetes insipidus. The classical eases of this disease in man were proven to result from an inadequate secretion of vasopressin, (ADH), normally caused by damage to the posterior pituitary, stalk or hypothalamus. This model was reproduced in the experimental animal by section of the pituitary stalk and damage to the ventral hypothalamus (supraoptic and paraventrieular nuclei). More recently, a nephrogenic type of diabetes insipidus has been uncovered in which the renal tubular epithelium appears to be refraetory to the action of vasopressin. There seems to be a hereditary basis for this condition.

The studies into the action of chlorothiazide stem from therapeutic problems encountered in the treatment of diabetes insipidus. The classical condition had been treated by replacement therapy in such forms as injectable pitressin tannate and snuff of posterior pituitary extract. However, some patients became allergic to the medieation, and others refractory to its action. It is also self-evident that nephrogenic diabetics cannot be maintained successfully on any amount of administered exogenous vasopressin.

Since a major complication of polyuria was a relative increase in serum electrolytes (hyperelectrolytemia), an attempt was made to induce an increased electrolyte excretion by using ehlorothiazide. The remarkable effects of this therapy were not only the expected return of serum electrolyte levels to normal, but a surprising decrease in fluid output and marked clinical improvement. These results seemed to follow a reduction in "free water clearanee", (the water excreted beyond that necessary to make the urine isotonic with plasma). Unfortunately, the antidiuretic effect of chlorothiazide is usually of a transient nature with the patients escaping, at least in part, from its action within a period of several days to a few weeks. The elucidation of its action is not only of academic interest but may also provide a basis for improvement of its therapeutic effect in this particular situation.

CHLOROTHIAZIDE

The object of our work was to loealize the diuretic action of chlorothiazide in the normal dog kidney and its antidiuretic action on the kidney of an animal with diabetes insipidus.

Normal Diuretic Action

To localize the effect in the normal kidney we used the selective tubular poisoning method of Dr. Nicholson. The first third of the proximal tubule can be damaged by potassium dichromate, and the last two-thirds by sodium tartrate. Both of these are administered by a perfusion of the renal artery. The distal tubule is damaged by a retrograde injection up the ureter of mercuric chloride. In each experiment only the left kidney was insulted; the right remained intact as a control organ. In each case, the dog was anesthetized two days after the kidney had been damaged and both ureters were exposed and catheterized. The animal was maintained on intravenous fluids and the urine collected for a period of not less than five hours. During this time half-hourly injections of Diuril "Lyovac"* were given. We wished to see if the left kidney with the selectively damaged area showed a quantitatively altered response in comparison with the normal right kidney.

After certain technical problems had been solved, a series of four experiments (for verification), were done for each of the dichromate, tartrate and mercuric chloride nephrotoxins. Study of the total urine volumes, osmolarities and electrolyte excretion patterns showed that mercuric chloride abolished the normal diuretic effect. Therefore, this action of chlorothiazide in the dog appeared to depend on an intact distal tubule.

Action with Diabetes Insipidus

The next step was to prepare dogs with diabetes insipidus by sectioning the hypothalamie-neurohypo-

* courtesy of Merck, Sharp and Dohme

physial tract and applying a coagulating current with a ball electrode to the ventral hypothalamus. Although Dr. Horsey has visualized and sectioned the pituitary stalks in at least eight dogs, none have shown overt clinical evidence of diabetes insipidus and most have died within a period of two weeks. At present we are reviewing our pre- and post-operative treatment programs with the hope that better care here may improve our results.

When we do produce diabetic animals we shall give them chlorothiazide with the expectation that it will ameliorate their polyuria. Subsequently, the various areas of the tubules will be selectively damaged as in the first part of the experiment. We expect that the toxic effect on one area will abolish the antidiuretic effect of chlorothiazide in that kidney. The area of antidiuretic effect may or may not be the same as the region of diuretic action.

COMMENT

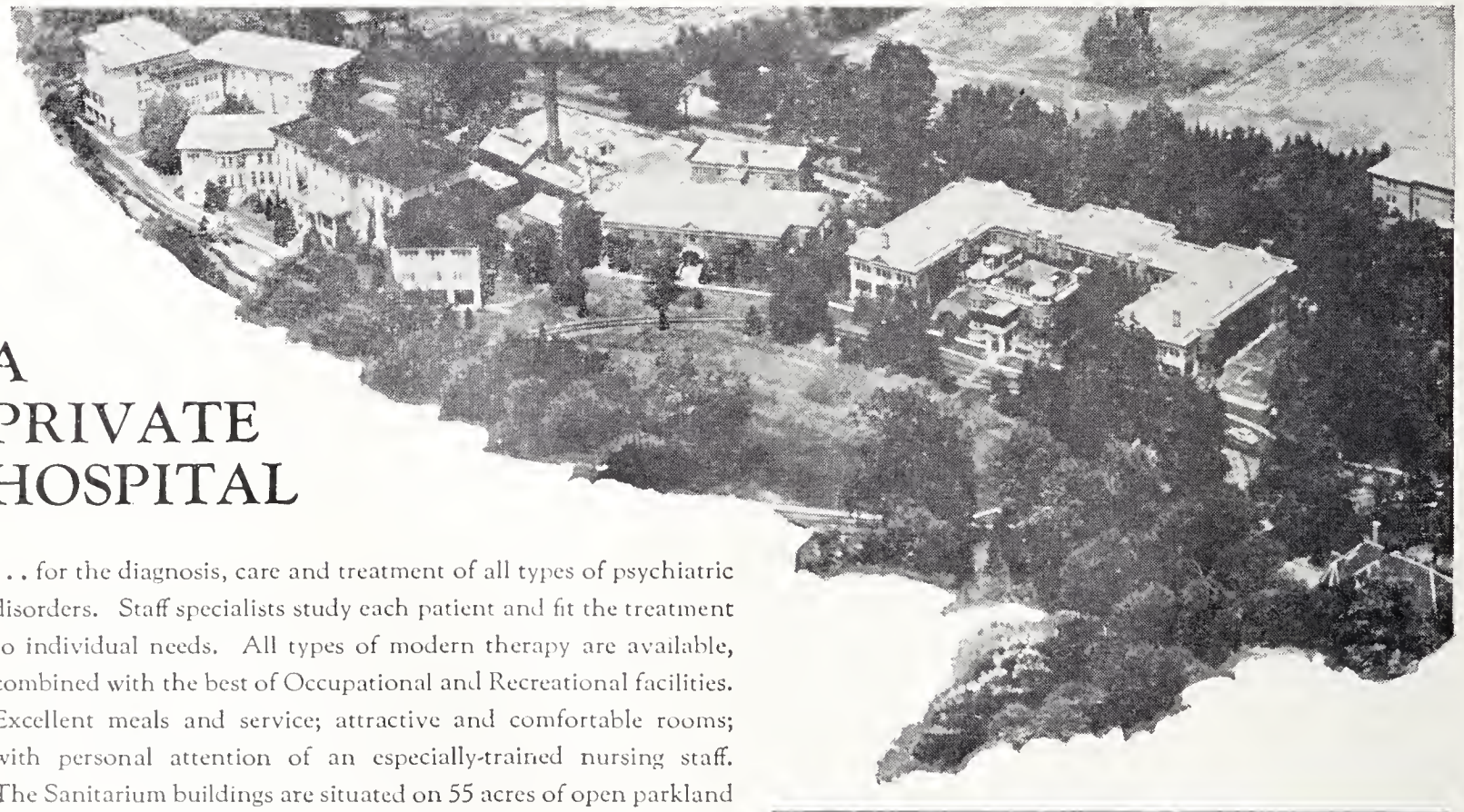
The two summers spent by the authors with this experiment have given them the opportunity to compare in vitro and in vivo experimentation and to note some of the difficulties inherent in biological work. The laboratory and operating room facilities of the Banting Institute were made available to them, and they gained an introduction to the techniques of experimental surgery.

ACKNOWLEDGEMENTS

The authors wish to thank Doctors Ezrin, Nicholson and Horsey for their interest and encouragement in this project.

REFERENCES

1. O'Doherty, N. J., Rosser, J., Slater, R. J., Canadian Medical Association Journal, 86:13:1962, p. 559
2. Ranson, Fisher and Ingram (The Hypothalamico-Hypophysial Mechanism in Diabetes Insipidus), "The Pituitary Gland" 1938, p. 410
3. Van Dyke, H. B. (Neurohypophysial Hormones), "Clinical Endocrinology I", 1960, p. 68
4. Leaf, A. (Diabetes Insipidus), "Clinical Endocrinology I", 1960, p. 73
5. Crawford, J. D. and Kennedy, G. C., Nature, 183:891:1959
6. Kennedy, G. C. and Crawford, J. D., Lancet, 1:866:1959
7. Crawford, J. D., Kennedy, G. C. and Hill, New England Journal of Medicine, 262:737:1960
8. Dingman, Benirschke and Thorn, American Journal of Medicine, 23:226:1957
9. Nicholson, T. F. and Downs, C. H., Can. J. Biochem. and Physiol., 35:641:1957
10. Keller, A. D., Endocrinology, 30:408:1942



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Recent Advances

CLINICAL APPLICATIONS OF HUMAN CHROMOSOME STUDIES

Recent advances in human cytology have revolutionized the field of medical genetics. Shortly after Tjio established the human chromosome number as 46 rather than 48 which was previously accepted as normal for many years, numerous reports of patients showing chromosome abnormalities began to filter through medical cytogenetic circles. The speed with which this new field has unfolded is largely attributable to improvements in investigative technique; more specifically the use of antibiotics in tissue culture, of colchicine to arrest mitosis in a stage suitable for chromosome study, and recent development of a method for culturing cells of peripheral blood which can now be subjected to chromosome analysis.

Soon a need for a system of numbering the 46 chromosomes became apparent, so that abnormalities could be reported and communicated to others with specificity. This need was stated in 1960 when at a cytogenetic conference in Denver, Colorado, it was decided that human chromosomes were to be divided into sex chromosomes X and Y and 22 pairs of non-sex chromosomes or *autosomes,* serially numbered in descending order of their length. The term "karyotype" which is in essence a chromosomal fingerprint, was defined as the systematic arrangement of chromosomes of a single somatic cell prepared either by drawing or photograph. The 46 chromosomes were divided into seven groups of morphologically similar chromosomes. Thus any individual chromosome being analyzed could with practice be placed into its correct group and be given its specific number.

Dr. P. E. Conen of the Hospital for Sick Children in Toronto has become deeply involved in the correlation of abnormalities found on clinical, laboratory, and chromosomal levels. Recently it has been shown that abnormalities of autosomes may produce marked congenital malformations, while in contrast sex chromosome abnormalities may be associated with very minimal physical changes. To date three autosomal trisomy syndromes (presence of a homologous chromosome in triplicate instead of usual paired arrangement) have been established; mongolism, D-1 trisomy syndrome (the extra chromosome is one of the chromosomes in 13-15 group), and No. 18 trisomy syndrome. In such trisomic states there is a triple dose of a *specific* set of genes rather than a double one. This understandably creates a genetic imbalance producing a *specific* pattern of anomalies which relate to the genes present in excess, thereby allowing for clinical recognition of the specific syndrome.

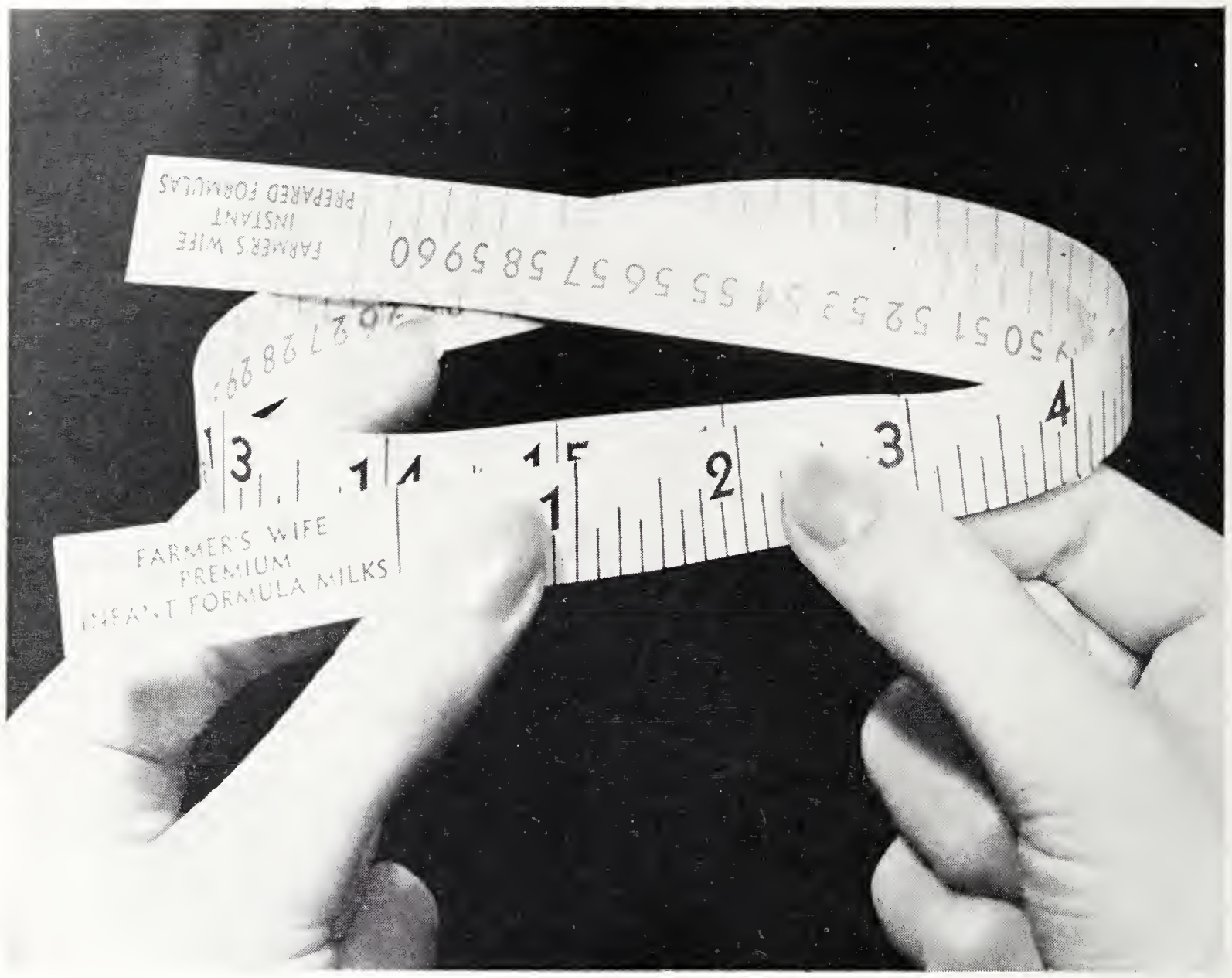
The first of these clinically important syndromes to be investigated at the Hospital for Sick Children was mongolism. This condition was found to be associated with trisomy of chromosome number 21 in a high proportion of cases. Dr. Conen's group has found chromosome analysis useful in diagnosis of mongolism specially when clinical features are not typical. Such a case was recently reported in a child of Chinese extraction.

The most recent autosomal trisomic state studied here is the No. 18 trisomy syndrome. In the past many infants were seen both clinically and at necropsy at the H.S.C. with mental retardation, hypertonicity, low set malformed ears, small mandibles and failure to thrive in terms of growth and development. It was not until a short while ago that chromosome studies on such infants elucidated the genetic bases of the problem; trisomy of autosome No. 18.

Chromosome analysis of sex chromosomes finds tremendous application in the field of inter-sex states, which appear not infrequently in psychiatric and endocrine clinics. Many such cases have been studied here. The XXY pattern of the Kleinfelter Syndrome, the XO pattern of the Turner syndrome, and a host of "mosaic" states only recently recognized, in which two or more populations of cells some showing normal karyotypes and others showing abnormalities in their sex chromosome content are seen. To date a great number of variations have been reported. Chromosome analysis serves as a useful adjunct to the sex chromatin test of Barr which as a result assumes even greater importance as a diagnostic test in suspected inter-sex states, and in screening large populations for sex chromosome abnormalities. It has wisely been suggested that the long ponderous names of many of the inter-sex states be dropped in favour of a more explicit nomenclature in terms of karyotype. Thus chromatin positive Kleinfelter's becomes XXY.

Although the field of human chromosome analysis is in its infancy, it has already added much to enrich and fortify medical knowledge. There is a strong tendency for theory and research of to-day to become the routine of to-morrow. To this tenet human chromosome analysis is holding true.

H. Tanzer 6T4



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Take Three Giant Steps Backwards

S. Mintz 6T3
K. H. Norwich 6T3

The authors take a critical look at the present analytic method of medical research and, finding it unequal to several important tasks, suggest a different approach.

It is a fact that ever since the first little bug crawled under the lenses of Louis Pasteur, about ninety-five per cent of the efforts of medical scientists has centered upon the *analysis* of biolgical superstructure into its component elements: anatomy to histology to cytology; pathological anatomy to histopathology; genetics to cytogenetics. Biological chemistry has stressed for example the qualitative and quantitative analysis of body fluids, and the analysis of protein into its component amino acids. With the use of microscopic and analytical techniques, we have succeeded in *curing* many diseases of bacterial etiology, in *preventing* many diseases of viral etiology, and in *compensating* for many diseases of endocrine aberration. But the efficacy of the microscopic and analytical techniques to the medical treatment of malignant, psychiatric and degenerative disease has remained inadequate. It may transpire that by persistance in the application of existing methods and ideology we shall conquer even these giants. We wager millions of dollars and millions of man-hours each year that such will be the case. But perhaps something totally new must be added; a concept newer than sepsis or circulation to the worlds that preceded them. In the reflection of this possibility, we invite you to step back, and examine in a new perspective some of the concepts we use uncritically in medicine and biology.

It is interesting to observe that while modern medicine first took shape under a microscope, modern physics began through a telescope. One of the first major achievements in physics was the formulation, by Newton, of his Laws of Gravitation — based experimentally upon the earlier astronomical observations of Kepler. And although Newton's Law serves to describe with a high degree of accuracy the orbits of the planets, it does *not* in any way depend upon the properties of the atoms or molecules of which these planets are constructed. Indeed, it was over two hundred years after Newton died that the submicroscopic particle assumed its mathematical morphology — as a sophisticated gathering of electromagnetic waves. For about half a century physics has continued its development both from the macroscopic and microscopic levels, and even the year 1962 finds a persistence in the dichotomy of the macro — and microcosmos. By analogy, how presumptuous looms the science of Medicine, which endeavours to explain and control the gross clinical disease processes wholly from the vantage-point of the microscopic, and with none of the thrust afforded by laws governing organisms as wholes.

The Analytic Process

Let us first examine the fundamental processes of current medical thinking. To be exact, let us analyse the process of analysis, using diabetes mellitus and elevated blood sugar concentrations as an example. The process of analysis is just a process of continued abstraction. First we express the disease as a malfunctioning of an organ, namely the pancreas. We then express the malfunctioning of the organ, as a function of a tissue or parenchymal constituent of that organ, namely the islets of Langerhans. We then express the malfunction of tissue as a function of constituent cells, namely the beta cells. We then express the malfunction of cells as a function of a chemical substance which they elaborate, namely insulin. We can then express the basic clinical problem as a function of the elementary chemical substance. That is, we relate the elevated blood sugar levels to the malfunction of (deficit of or antagonism to) insulin. If we are Banting and Best, we will now compensate for the biochemical defect by continued exogenous control. But while we have compensated for the defect, we have not cured the disease, we have not discovered its etiology and we cannot usually prevent its occurrence. Figure 1 summarizes these processes of thought. Notice the convergence towards a focal point.

It is apparent that the medical treatment of most diseases is centred upon the correction of a basic biochemical disorder. If this biochemical disorder is thoroughly corrected and does not recur upon the withdrawal of exogenous medical intervention, then the disease is "cured". But very seldom is this magnificent end achieved. The reason is apparent. While the basic biochemical disorder is causative of all the pathology which lies above it on the "pyramid", those factors which are causative of this biochemical dis-

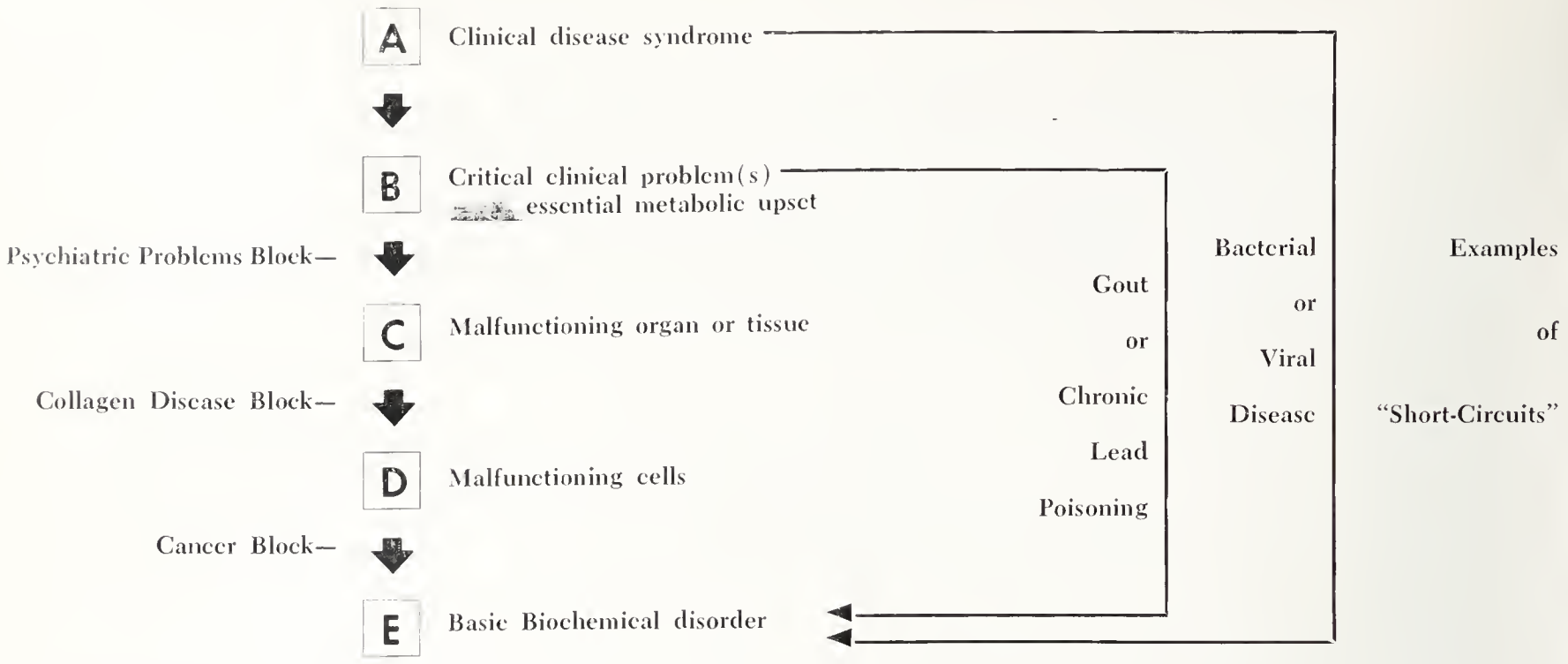


Figure 1: The Pyramid of Analysis
The investigation of most medical diseases has followed the pattern A→B→C→D→E.

eg.	diabetes mellitus and diabetes insipidus	hepatolenticular degeneration
	hyper and hypothyroidism	phenylketonuria
	hyper and hypocalcemia	erythroblastosis fetalis

Certain diseases have yielded to a short-circuiting of this process of reasoning, eg. chronic gout where it seems that the basic biochemical defect may be rectified without knowledge of the instigating pathological tissue.

Certain diseases have not yielded completely to this analytical approach, and where the analytical process has been stopped we have indicated this by "block".

order, and which are themselves biochemical factors, are still totally or partially unknown. And so follows the conclusion which has occurred to all of us at one time or another: "the basic biochemical disorders can never be thoroughly understood — and hence most diseases never cured — without the complete elucidation of all relevant normal biochemical reactions, pathways, syntheses, and their interrelationships." For the above reasons, whether stated explicitly or whether assumed implicitly, the great majority of present day research is conducted at a biochemical level.

But is this the only approach to the problem of disease? Or are we trying to deduce our "Laws of Gravitation" solely from the properties of the atoms composing the planets? Such is the central theme of this essay.

Biological Laws

Biological laws are few and of poor quality. You probably know them all but you do not think of them as laws. For example you may recall from embryology "Ontogeny begets Phylogeny", — an axiom whose excellence of poetry is surpassed only by its uselessness. J. W. N. Sullivan observed that "we apparently can not even generalize the statement that 'all men are mortal' into 'all living things are mortal' for it appears that the amoeba eludes this law."[1] The same author later compares the doctrine of Natural Selection and the Mendelian Theory of Inheritance (both biological laws) to the Ether Theory of Light: theories that may prove their merit, but will probably be superceded. One of the few good attempts at formulation of a biological law was made by Claude Bernard (without reference to whom no biological manuscript is deemed complete), whose theory of constancy of 'milieu interieur' has been held in great respect. In fact this theory — that any organism 'attempts' to maintain the constancy of its internal environment — is but a particular example of teleological reasoning to 'explain' physiological events. Nevertheless it *is* a biological law which permits us to predict the outcome of certain physiological and biochemical reactions without necessarily knowing the intermediate reactions. For example, if we raise the plasma pH of an experimental animal by intravenous injection of $NaHCO_3$, we can predict that within a short time, the pH will drop to its normal physiological level. We can make this prediction with no prior knowledge of the intermediary homeostatic mechanisms such as buffer reactions.

Ideally, we should be able to divide the science of biology into theoretical and experimental biology. However, we have not been able to encompass all of biology

into a theoretical network; the reason for this is two-fold. Firstly, we are now living through a golden age of technology. There is far greater emphasis placed upon technological advance than upon theoretical. Secondly, those biological laws which have been established, do not permit one to continue in a process of chain reasoning. Each biological principle stands aloof and does not depend on any other. Thus a text of biological theorems, analogous to Euclidian theorems, remains impossible, and each new "law", must barge into the mind of its inventor like a bolt from the blue.

"Disease"

We should now like to introduce Clinical Philosophy, a monumental new addition to clinical medicine. We shall entitle our first session on Clinical Philosophy; "What is a Disease?" Certainly if we are to cure disease, it is expedient to know exactly what "disease" means. Dorland's dictionary defines "disease" as "a definite morbid process having a characteristic train of symptoms."[2] It then defines "morbid" as "pertaining to . . . disease." Suffice it to say that disease is that which is characterized by a train of symptoms (and signs). In other words, a disease is *defined* by its syndrome of symptoms and signs. In earlier days of medicine, most disease syndromes were sufficiently distinct that the independent identity of each syndrome was unchallenged. Small pox and big pox were adequate criteria for distinguishing Variola from Syphilis. "Bright's Disease" could mean only one thing. But today we are perplexed with serological tests, radiographs, and tissue biopsies, and few symptom-complexes are permitted to fall so neatly under one heading. For instance, consider two patients who present with general malaise and a widespread maculo-papular rash. Their signs and symptoms are identical. Have they the same disease? According to our agreed definition we must say "yes". But during the convalescent period, serological tests show unmistakably that one case was due to ECHO virus type 9, and one to Rubella. Surely the same disease cannot be caused by two different etiological organisms. Or can it?

Another patient has notably tight, shiny skin and some limitation of movement. She complains of myalgia and dysphagia. General signs and symptoms are suggestive of a collagen disease. The diagnosis: scleroderma — or dermatomyositis — or "sclerodermatomyositis".

Finally, a child with no history of glomerulonephritis, presents with generalized oedema, proteinuria, hyperlipemia and hypoproteinemia — undoubtedly a nephrotic syndrome. However "nephrotic syndrome" is not a disease but a collection of diseases. On the basis of tissue biopsy and electron micrographs we may diagnose subacute glomerulonephritis, or lipoid nephrosis. But if we are permitting the analysis of one eclectic disease into its component diseases on the basis of electron microscopy, then surely the next stage is to subject all other "diseases" to this scrutiny. Thus we shall subdivide peptic ulceration into twenty or more varieties on the basis of variations in electron micrographs. "But," you object, "there was reason for such a subdivision of nephrotic syndrome because each subdivision has a different prognosis, while the prognosis of peptic ulcer is unlikely to correlate highly with its microscopic appearance." But, we counter, this justification must mean that your definition of disease will depend on the prognosis of this disease — which is certainly paradoxical.

In summary, our current usage of the term "disease" is not consistant with any single definition. Diagnostic sophistication has so broadened our knowledge of disease, that the originally distinct boundaries between diseases are fading and may be replaced by arbitrary divisions. More rationally, they will change as the electron orbits did — into orbitals of uncertain delineation. Disease syndromes will merge one with the other, will cease to be named individually, and clinical emphasis will be placed solely on the totality of the patient's symptom-sign complex.

Classifications of Disease

We have discussed the definition of disease, but what about its classification? The standard mnemonic classification (if you need reminding) goes something like this:

A	Congenital		
B	Acquired	1. Traumatic	5. Allergic
		2. Inflammatory	6. Psychiatric
		3. Metabolic	7. Neoplastic
		4. Degenerative	

No classification of disease is perfect, nor do we expect this one to be. The great danger lurking in any classification is that it imposes its philosophy on its user. For instance, this classification insidiously erects barriers artificially separating these types of disease. And these barriers dominate our mental attitude until they unconsciously rule our thinking. Let us illustrate.

Schizophrenia was long considered one of the strictly psychiatric diseases, and was investigated and treated as such, with psychotherapy and so on. Lately, evidence has been accumulating that this psychosis has a "metabolic" aspect — for instance "recently reported is a *blood* factor in schizophrenic patients that will produce a psychotic reaction in normal individuals."[3] While this has not yet been confirmed, it is

certain that much time has been lost in the study of schizophrenia while it has been investigated as a purely psychiatric disease, with its metabolic aspects ignored. Had schizophrenia not been left solely to the tender mercies of the psychiatrics, the biochemists might have approached the problem much sooner.

Medicine Under a Macroscope

Accompany us on a trip in time back into the eighteenth century. Put yourself in the position of a physician of this age. This physician is presented with three cases. In the first case the patient has a high fever, a rusty sputum and râles in his chest. In the second case the patient has convulsions and focal neurological signs. In the third case the patient has a circumscribed painful swelling on the back of his neck. To the physician of the day these patients are suffering from diseases which have absolutely no common denominator. Yet from our vantage point in the twentieth century, with our knowledge of bacteriology, we establish the diagnoses as pneumococcal pneumonia, staphylococcal brain abcess, and furuncle respectively. Thus in our world it is not inconceivable that quite different clinical manifestations be caused by the same sort of agent: bacteria. Now having travelled with us to the past we invite you to look ahead into the future. The physicians of the twenty-second century may look back upon us and say "the people of 1962 lacked such a very basic concept. How could they have hoped to discover the etiology of 'cancer' as they called it?"

To bring us back to the present, allow us to consider another example: dermatomyositis. This disease has a neoplasm associated with it in seven to fifteen per cent of cases.[4] The neoplasm may be in the stomach, breast, lungs, or almost anywhere. But most surprisingly, the dermatomyositis may occur before the cancer makes its appearance. Resection or suppressive treatment of the tumor often causes an improvement in the dermatomyositis. Rather than saying that this disease is due to auto-immunity or collagen disease, let us postulate a new idea. Suppose some etiological 'principle' exists which can manifest itself as either cancer or a skin and muscle lesion. This concept is as alien to our thinking as was that of a common etiological agent to neurological disease and lobar pneumonia. This idea is introduced only to show the *kind* of thinking which is necessary to formulate an entirely new theory of disease. And perhaps the lack of this thinking accounts for our lack of success in cancer research.

This brings us back to the main theme of the essay. There are basically two directions in which medical research can travel. It can move in the direction of increasingly more concise definition of individual disease syndromes, so that we have at hand a mass of detail about every disease, investigated independently from all other diseases. Or it can consist of the integration of such data in a logical manner in order to formulate broad new concepts or re-evaluate old ideas. Ideally, the two approaches are interrelated and complementary; unlimited progress in either one is impossible without corresponding progress in the other. Yet a casual perusal of medical literature will show that the emphasis to-day is focussed almost entirely on definition of details of disease, to the exclusion of the integration of already-accumulated data.

Practical Suggestions

We should like to offer a few simple suggestions which may help to give us all a larger view on medicine. We start, as all doctors do, at medical school. Here we gain knowledge, but we also form attitudes which last all our lives. For instance in all reputable medical schools, emphasis is placed on the students' memorizing a fairly heavy load of facts, without any incentive given for original thinking. Now certainly one must memorize some facts, at least enough to establish clinical proficiency and to form a basis for future conjecture. But we are required to memorize so much, that instead of being given a glimpse of the vast uncharted sea of medical knowledge, we are held to a course where seemingly all shoals are known. And to help keep us in these "known" waters, we are given attitudes and pidgeon-holes in the form of mnemonics and "aids" to study.

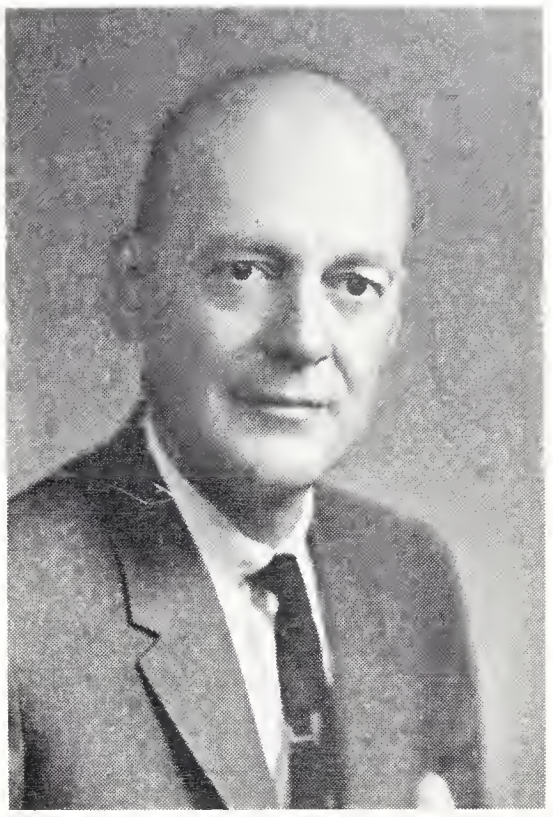
What can we do about this? Several suggestions have been made elsewhere, and these we shall only list. Rearrangement of the traditional pattern of courses is one suggestion, and various schemes have been proposed, some of which have merit. One plan would have the premedical subjects (English, Logic etc.) spread out over the entire six years rather than having them telescoped into two years' work, to be forgotten almost immediately. One school teaches medicine by working right through each system of the body in turn. For example in first year, gastrointestinal anatomy, physiology, pathology, medicine, and surgery might all be taught, thus reducing the quantity of rote memorization and increasing the possibilities for association and deduction.

Another approach to this problem is culled from history. Pasteur, a chemist, formulated the bacterial concept of disease; Helmholtz, a physicist, founded ophthalmology. Engineers and statisticians have contributed immeasureably to medicine in the past fifty years. The lesson is clear: people from other disciplines should be enticed into medicine, where their fresh approach may stimulate radical new discovery.

See page 31

Profiles

Dr. J. D. Hamilton
Dean of Medicine,
University of Toronto



Photograph by Ballard & Jarrett

In following the careers of successful men, one often asks them whether they had a specific goal which they had set for themselves, and which has guided their efforts in the past. Dr. Hamilton has always had one such goal: the desire to do excellent work, whatever field he is in.

He was born in 1911 in Revelstoke, B.C., a town of 3,000 people, where his father had a thriving general practice. On finishing high school there, he decided to go on to medicine — the work which he had come to know and admire. He enrolled at the University of Toronto, where his father had graduated, but found his early medical studies somewhat less appealing. This feeling did not prevent him from attaining first class standing, but it did create some doubt in his choice of a career. However, in his third medical year he became fascinated by medicine and pathology, with the variegations and complexities inherent in these subjects. His choice was made, and he graduated with honours in 1935, to an internship at the Toronto General Hospital. During his university years he played in the Hart House Theatre, and studied languages — for he was determined to travel. To that end, he mastered French and Italian.

His interest in Pathology grew during his junior internship. After demonstrating in that subject at the University of Toronto, he left for England, where he continued doing so at Cambridge for two years. He travelled through Europe on long leaves, finally satisfying his wanderlust. He then returned to take an assistant residency in Pathology at Johns Hopkins. Following the outbreak of World War II he joined the Royal Canadian Army Medical Corps for overseas duty. With Dr. Chute, he worked on the new techniques of casualty therapy using penicillin. Much of this work was done at the Italian front.

After the war, Dr. Hamilton was an Assistant Professor of Pathology at McGill for one year, and was then appointed as Professor to head the Pathology Department at Queens until 1951. He then took the same position at the University of Toronto, which he held until his appointment as Dean of Medicine in 1961

Apart from his present post, Dr. Hamilton has many honours to his credit including membership in the Alpha Omega Alpha Honour Medical Society and many professional societies. He is Honorary Consultant in Pathology to several hospitals. His scientific research was done mainly on arteriosclerosis and hypersensitivity, and he has published many papers in these fields.

Dr. Hamilton was married soon after the war and has four children — three girls and a boy. He skis at Collingwood with his family, enjoys the theatre, good food and good wine, and also plays a bit of golf. His own very personal interest outside of medicine lies in archeology and ancient mythology and he speaks of these as one might of an old and highly respected friend. He has indeed many interests, but to all of them; medicine, his faculty, and his students, he brings in the words of a close friend "the greatest sense of serious responsibility and a vast personal generosity."

Jarda Polak 6T4

Conclusion

Now look again through your microscope, back into the world of the particulate and the analytical, but approach your work with a tempered enthusiasm, for you are now keenly aware that these tiny specks that are decorating your retina form only a fragment of a design which is greater by a million magnitudes. And all specks, although governed individually by physical-chemical laws, function harmoniously in this greater design, much as electron particles sketching patterns on a picture tube.

REFERENCES

1. Sullivan, J. W. N. The Limitations of Science — Mentor Books 1949. — Viking Press 1933.
2. Dorland's Illustrated Medical Dictionary. Edition 23 — Saunders — Philadelphia 1957.
3. Harrison, T. R. Principles of Internal Medicine. Edition 4 — McGraw-Hill — 1962.
4. Cortes, F. M. et al. American Journal of Medical Science. 243: 77, 1962.

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Vascular Changes in Inflammation

William J. Weiser 6T4

Having designed his own rabbit ear chamber, the author has described normal vascular tissue growth as well as vascular changes in non-allergic and allergic inflammation.

INTRODUCTION

The study of blood vessels is fundamental to pathology. A wide spectrum of conditions ranging from inflammation to the so-called collagen group of diseases involve significant vascular lesions. Much investigation is now centered about the pathogenesis of the various necrotizing angiitides[29], of several glomerulonephritides[13,27], and of other pathologic conditions involving blood vessels[13,24].

The in vivo study of blood vessels has been hindered largely by the technical difficulties encountered in isolating a living vascular tissue which is thin enough for light microscopy and which will remain intact through long periods of observation.

Since the work of Cohnheim[2] and Zeigler[10], E. R. Clark[4] and J. C. Sandison[19,20] had employed a technique of inserting a light-weight transparent chamber into a rabbit's ear, and of observing the vascular tissue that grew into the chamber. (See figures 1 and 2 for the technique of construction and insertion of the chamber.)

Growth of vascular tissue into the chamber

In the chambers constructed by us, and in those observed by others, blood vessels first appeared around the periphery of the central viewing table of such a chamber at seven days, and the growth completely covered the table at four weeks. Immediately after the operation, the central viewing table is covered with coagulated plasma, tissue debris (including bits of epidermis not completely cleared from the pinnial

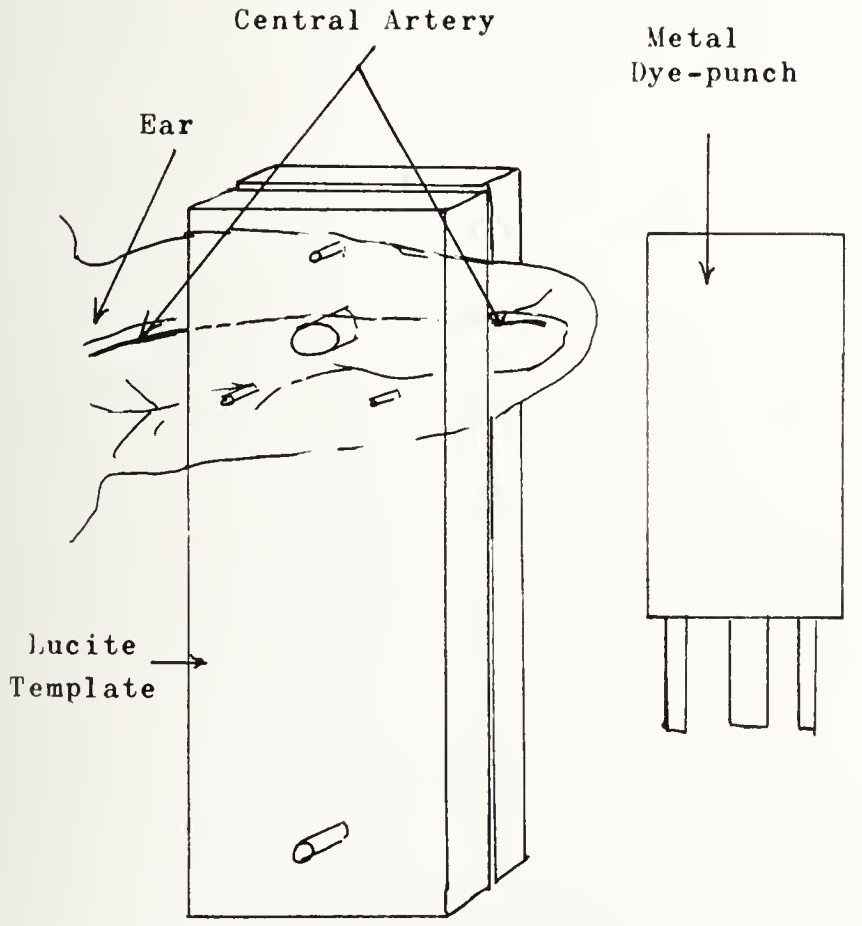


Figure 1. Illustrated here are the lucite template and the metal dye used to punch four holes through the rabbit's ear. The chamber is then inserted into the holes and bolted to the ear.

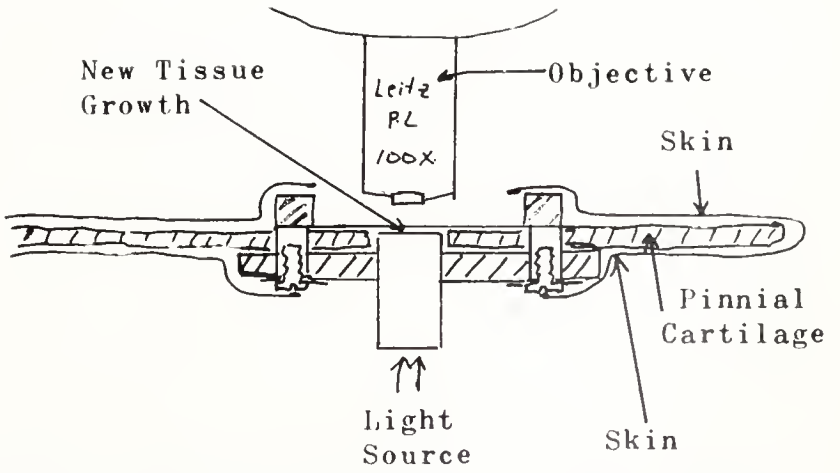


Figure 2. The rabbit ear chamber is shown in section, inserted into the ear. The chamber has two parts, a mica coverslip mounted in a lucite ring, and a lucite baseplate. The two parts are bolted to each other through the rabbit's ear.

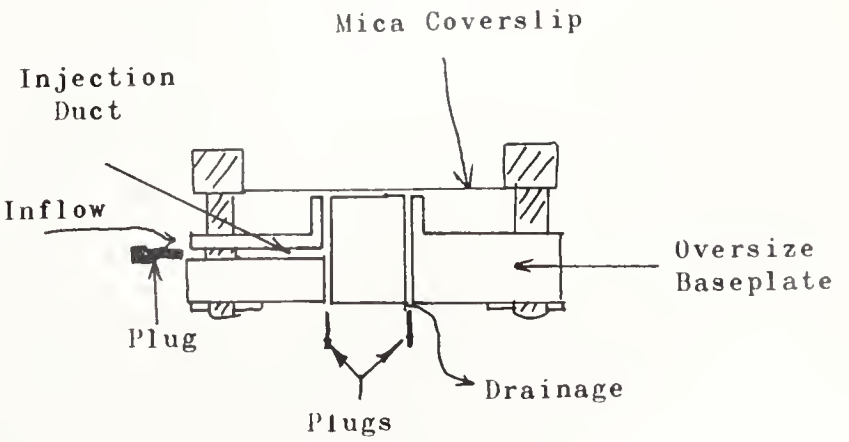


Figure 3. Perfusion chamber.

cartilage) and extravasated blood cells. Within a short time tissue macrophages are seen at the periphery of the table, and within six to seven days fine loops of newly sprouted capillaries are seen over the edge of the table closest to the central artery. Preceding these capillary loops is a narrow zone of pulsating plasma, and preceding the plasma is a row of actively ingesting macrophages. Although others describe only a zone of pulsating plasma, we observed this pulsation to often cover the entire viewing table at 4-5 days, and chambers showing this had the earliest and most extensive capillary ingrowth.

The pattern of anastomoses of the newly formed capillary loops, and the organization of some immature vessels into 'nutrient' arterioles and draining venules are dynamic processes which vary with the local needs of the tissue, the local hemodynamics, the temperature of the chamber and ear, and mechanical pressures exerted on and by the growing tissue.

Certain vascular channels carrying and draining the majority of blood became differentiated into arterioles and venules, the venule usually lying alongside its arteriole. Other smaller channels carrying less blood decrease in size and numbers and are eventually replaced by fibrous tissue. The "adult" pattern as conceived by Clark consists of a gel-like moderately vascular connective tissue with a major arteriole (arterioles) which remains macroscopically unchanged for months, and its accompanying venule which is seen to undergo more frequent changes. This "adult" pattern can be observed for hours at a time, every day, for periods of over a year, without any adverse effects on the rabbit or the chamber tissue.

The local pattern of early blood flow in the newly grown tissue partially determines the "adult" plan. It was observed by us and others that only a few of the many capillaries are carrying blood at any one time, and the speed of circulation in these capillaries seems to be constantly varying, but prolonged cessation of circulation was never observed by us in a normal chamber. Prolonged cessation, as observed by Clark and Clark[3], apparently a result of a shift in the local blood flow, precedes the disappearance of the involved vessel. The walls of the vessel appose each other, the vessel fragments and loses contact with others, and the isolated portion disintegrates into protoplasmic blobs which are phagocytized and removed.

Cellular components of the chamber[19]

Endothelial cells of the newly formed tissue were seen to arise only from endothelium of preformed tissue; and these endothelial cells have capacious to narrow nuclear areas, and their nuclei are seen to migrate along the vessel wall.

Perivascular cells, presumed to be of mesenchymal origin, line the newly formed capillaries. Young perivascular cells have a humped perinuclear region and long cytoplasmic processes which follow the contour of the vessel wall and often enrap the vessel, whereas older cells have a less humped perinuclear area and shorter cytoplasmic processes. These perivascular cells which are also seen around the smooth muscle of arterioles and venules and which decrease with the age of the vessel, play no known part in capillary contractility.

Perivascular cells disappear from the vessel before it becomes an arteriole. A new layer of cells appears and runs transversely to the long axis of the vessel. The function of these cells is unknown. Still later focal areas of smooth muscle cells are seen, and these are responsible for focal contractions of the developing vessel.

IN VIVO OBSERVATIONS

Normergic vascular response

The response of blood vessels to normergic inflammation has been well described[2,3,14,15,21]. Local mechanical trauma, heat and chemical agents all produce a similar sequence of events varying more in quantity than quality. The ability of endothelium to respond to disturbing stimuli is limited; it may undergo proliferation and/or swelling as in glomerulonephritis, or it may become necrotic as in necrotizing arteritis and necrotizing arteriolosclerosis. Carbon particles injected in sterile saline were seen to cause little or no endothelial stickiness and no leukocytic adhesion. However, croton oil, an agent highly toxic to tissue, when injected into the chamber leads to varying degrees of endothelial stickiness, leukocytic adhesion, capillary dilatation, stasis, leukocytic emigration and RBC extravasation, and in extreme instances, vessel disintegration[3]. Clark et al[3] consider the endothelial response to nonspecific trauma to fall within two basic categories; the recoverable and the irrecoverable stages. Once local capillary dilatation or collapse occurs together with massive RBC and WBC extravasation, the vessel irreversibly fragments and the endothelium disintegrates.

As observed by us and others, the flow of blood is laminar (plates 1 and 3) and in larger vessels a definite clear plasmatic zone (plate 3) is seen adjacent to the endothelial lining (plates 1 and 4). White blood cells have a tendency to travel in this clear zone and roll along the endothelium, frequently adhering to it for a few seconds and then pushed along again by the steady stream of plasma (plates 1, 3 and 4). In inflammation the endothelium is presumed to become

KEY

LA Leukocytic adhesion

HM Histogenous Macrophage

EN Endothelial Nucleus

PS Plasma Skimming

EL Endothelial Lining

CLS Circulating Leukocytes

RBS Red Blood Cells

TF Turbid Flow

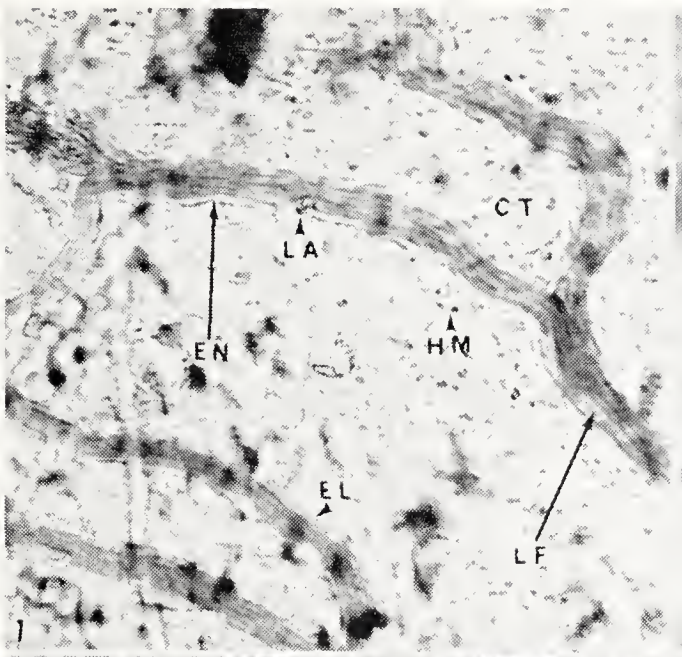
LAS Leukocytic Adhesions

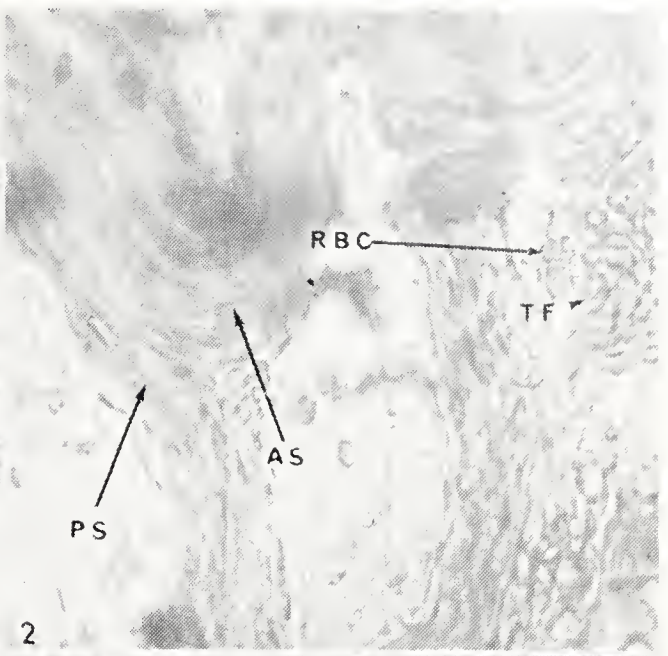
CPZ Clear Plasmatic Zone

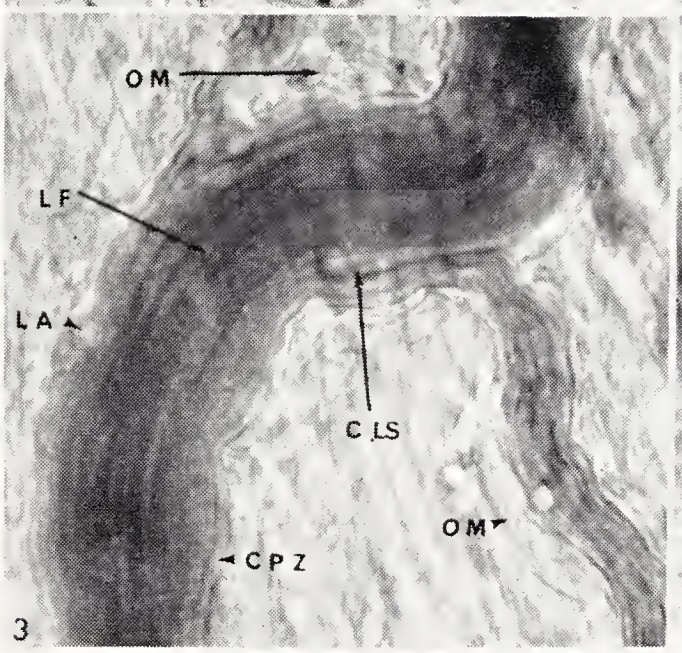
OM Perivaseular Cells (or perhaps organizing musele)

LF Laminar Flow

AS Axial Stream







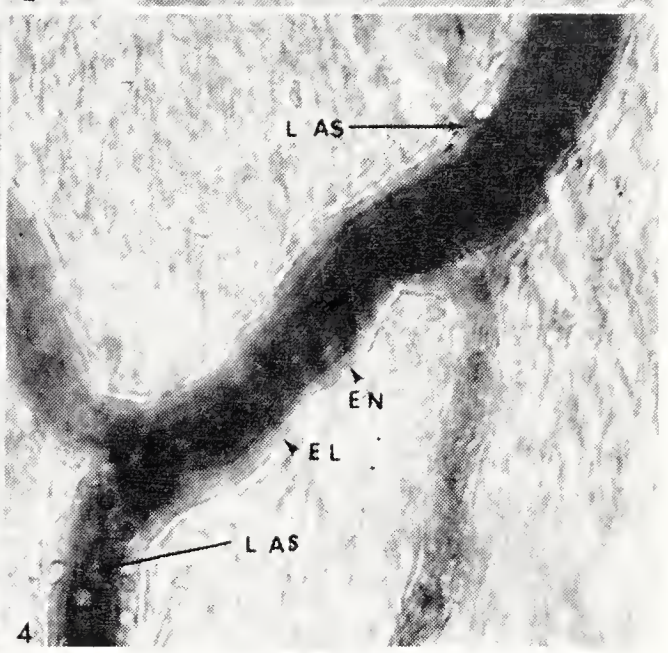


Plate 1. Low power photograph of a normal chamber tissue. A network of vessels, probably capillaries, is shown in a fibrous tissue matrix. This photomicrograph illustrates the type of living granulation tissue that grows into the chamber by one month. (x100)

Plate 2. A high dry photograph of a larger vessel and its smaller tributaries. Laminar and turbid flow, axial streaming, and plasma skimming are shown. (x350)

Plate 3. A larger vessel, perhaps a venule, is seen under high dry magnification. The clear peripheral plasmatic zone is shown with leukocytes tending to circulate there. (x350)

Plate 4. The refractile endothelial lining and nucleus are clearly illustrated under high dry magnification. Leukocytic adhesions are also seen and in this case are likely due to mild inflammatory changes from handling of the rabbit ear chamber. (x350)

stickier than normal because of the increase in number and length of contact of the leukocytes adhering to the endothelial lining. There is no apparent change in the nature of the leukocyte itself.* The increased duration of contact between a leukocyte and a damaged endothelial lining leads to a greater WBC emigration. Pre-stasis and stasis play a major role in this leukocytic emigration as the reduction in flow allows more leukocytes to come in contact with the vessel wall for a longer time.

*Stehbens and Florey[21] found no difference in the stickiness of endothelium to carbon particles in the normal or inflammed state; but in inflammed vessels, thrombi composed of platelets and carbon tended to stick to leukocytes adherent to the endothelium. McCutcheon[2], however, states that both endothelium and leukocytes become sticky in inflammation.

Allergic Vascular Response

The ear chamber technique has been used to study tuberculous infection[7,8] as well as the vascular responses in the serum sickness type of hypersensitivity (1 and 9) state.

Germuth[11], and Dixon et al[6] have shown that following the intravenous administration of a foreign protein three phases of elimination of this antigen occur, and when free circulating antigen is eliminated from the circulation, free circulating antibody can be detected. The first phase of elimination is in an equilibration of the antigen between the extravascular and intravascular fluid compartments, the second is a non-immune normal catabolism of the foreign protein; and the third is a rapid immune elimination of the protein

thought to involve an antigen-antibody interaction. The lesions of serum sickness are seen during the immune phase of antigen removal and reach a maximum at the completion of this phase.

Five to seven days after the initial injection of horse serum into a normal ear-chamber rabbit, a time when antigen and antibody (probably in a combined form) are both in the circulation, the following vascular responses have been observed:

Vascular: Arteriolar constriction was observed.

Intravascular: Sludging of RBC's and WBC's was seen and platelet thrombi and emboli formed.

After the second intravenous injection of horse serum into a previously injected rabbit, the following responses were observed:

Vascular: A temporary constriction of the arterioles feeding the central table occurred which was followed by localized constrictions and dilations of the vessels over the table. During the first week after the second injection the endothelium, in dilated arterioles with rapidly flowing blood, was swollen.

Intravascular: Platelet and WBC thrombi and emboli, and RBC sludging were more frequently seen.

Exudate: Emigration of WBC's through the venule and arteriolar endothelium was seen only after the second injection.

Arterial Spasm: This was seen maximally after the second injection of horse serum and was followed by endothelial damage and vessel dilation.

An allergic origin of these vascular responses is probable. Firstly, the 5th-7th day responses occur during the 'primary immune response' of the animal to a foreign protein. During this time antigen and antibody are in circulation, probably in a combined antigen-antigen complex. Others using a similar technique, reported arteritis[16], myocarditis[17], nephritis[27] and synovitis[18] 6-10 days after the initial injection of a foreign serum into rabbits. Secondly, the most severe vascular responses occurred after the second injection of horse serum ('secondary immune response'). It is known that a single injection of antigen primes the antibody producing mechanism of the body such that a subsequent injection of the same antigen leads to a more rapid rise and a greater degree of antibody production[17]. It is also felt that the nature of the secondary-antibody may be qualitatively different from that of the primary-antibody[12].

In the light of the above observations, an interpretation is given to account for the vascular changes recorded. During the 5th-7th day period, circulating antigen-antibody complexes, either directly or via a physiologic chemical mediator(s), are responsible for the vascular responses seen. The greater quantity and different quality of antibody formed during the secondary immune response of the animal, admits the possibility of a different antigen-antibody complex (qualitatively, and quantitatively as far as antigen/antibody ratio and amount are concerned) in the circulation. This different complex may lead to a more severe vascular reaction. It is also possible that the primary immune response to a foreign serum primes the tissue sites making them more susceptible to further antigenic stimuli, or that local antibody-producing cells develop at target sites after the initial antigenic stimulus, and that the local antibody produced at these sites after a second stimulus may have a greater affinity for circulating antigen, or may so alter the antigen-antibody complex arriving there from the circulation that a more severe local tissue response is produced[22].

The preceding interpretation agrees with the work of others who have shown the phlogistic nature of soluble antigen-antibody complexes in antigen excess in the rabbit's skin[5], its necrotizing action on liver parenchyma[23], its anaphylactogenic property in mice[25], and its ability to initiate the Schultz-Dale reaction in normal guinea pig smooth muscle[26].

SUMMARY

The importance of blood vessels in pathology has been emphasized, and a method of observing vascular responses in vivo has been briefly presented. Many of the observations cited were confirmed by us in chambers built by the author. Emphasis has been placed on the vascular responses in allergic inflammation and an explanation of the mechanism offered in the light of recent studies in immunopathology.

ACKNOWLEDGEMENTS

I wish to thank Doctors Movat, Steiner, Fernando, van Erkel and Col. Pearce for their assistance in this endeavour and Mr. Günther Thomas for his invaluable aid in constructing and photographing the chambers. (All of Banting Institute; University of Toronto).

REFERENCES

1. Abell, R. G. and Schenck, H. P. — J. Immunol., Vol. 34, p. 195-213, 1938.
2. Anderson, W. A. D. — C. V. Mosby Co., St. Louis, Chapter 3, (by McCutcheon) Inflammation, 1961.
3. Clark, E. R. and Clark, E. L. — Amer. Jour. Anat., Vol. 57, p. 335-438, 1935.
4. Clark, E. L. and Clark, E. R. — Amer. Jour. Anat., Vol. 35, No. 3, p. 239-264 and p. 265-282, 1925.
5. Cochrane, C. G., and Weigle, W. O. — J. Exp. Med. Vol. 108, p. 591, 1958.
6. Dixon, F. J., Vazquez, J. J., Weigle, W. O. and Cochrane, C. G. Arch. of Path., Vol. 65, p. 18, 1958.

See page 42

Medical Horizons

Graduates of our Medical School are scattered throughout the free world. Now more than at any other time, undergraduates are also using summer vacations to apply their medical training in faraway lands. In this year's six issues, we hope to present thumbnail sketches of these truly interesting experiences.

Wm. S. C.

A SUMMER CLERKSHIP IN MALTA

It was my privilege last summer to work for a month on a medical ward in Saint Luke's Hospital, Guardamangia, Malta. This seven hundred bed hospital, the largest on the islands, is operated by the government in co-operation with the Roman Catholic Church.

The medicine practised here is of a very high calibre. The technical facilities may lag slightly behind what we would expect to find in a Canadian hospital of comparable size, but with regard to the clinical aspect of medicine, the Maltese stand very tall indeed. The bed-side teaching that I received in Malta certainly rivals the best that I have been exposed to anywhere.

The variety of disease to be found on a Maltese medical ward reflects the geographical position of this major port-of-call. My ward was a museum of tropical disease. Patients suffered from such infections as brucellosis melitensis, kala azar, tetanus, hydatid cyst disease, amoebiasis, dengue and typhoid fevers, as well as many of the more common North American infections. There was also one interesting case of Dercum's adiposa dolorosa which was thought to be secondary to a bomb blast injury.

The first patient assigned to me proved to be a pyrexia of unknown origin. If this symptom presents a diagnostic problem in Canada, in Malta the range of likely possibilities is considerably larger.

Leprosy is present on the islands and a separate hospital is provided for sufferers of this disease. Although not required by law to do so, many lepers reside here throughout the course of their illness, for the hospital is well-maintained and is set in pleasant surroundings.

The advent of insulin, superimposed on an isolated, intermarrying people, has caused a sharp increase in the incidence of diabetes mellitus among the Maltese, until at the present time one in ten of the islanders is a diabetic. The Maltese islands would then to my mind provide excellent material for research in diabetes and heredity.

Students of medicine in Malta require seven years to obtain their degree, two years of pre-medical studies and five medical years. In a course that commences once every three years, only thirty of the two-hundred and fifty freshmen are destined for graduation; Therefore, the failure of one subject can mark the end of a medical career. After graduation, the young Maltese doctor faces a rotating internship of three years duration.

Private practice still exists in Malta, although this is entirely due to the efforts of the doctors who, five years ago, staged and won a five-day strike against impending complete governmental control. At present, the Maltese government provides a District Medical Officer to each community, (a total of forty-two for a population of three hundred thousand), for the benefit of those who cannot afford private medical care. The D.M.O., in addition to his charge, can engage in an unlimited amount of private practice — a situation which one would expect to lead to many problems. However, in this small island, the remarkable success of this system is due to the high integrity of the doctors chosen as D.M.O.'s. Now, Malta is revising her national health plan on the advice of an external British commission, but the nature of the new plan is yet to be released.

No article about Malta would approach completeness without some mention of the rugged beauty of her high fortress-cities, the magnificence of her underwater scenery, and above all the open friendliness and generous hospitality of her people. These reasons, as well as the medical insight to be gained, make a summer clerkship in Malta a most worthwhile and memorable experience.

Roger Ball 6T3

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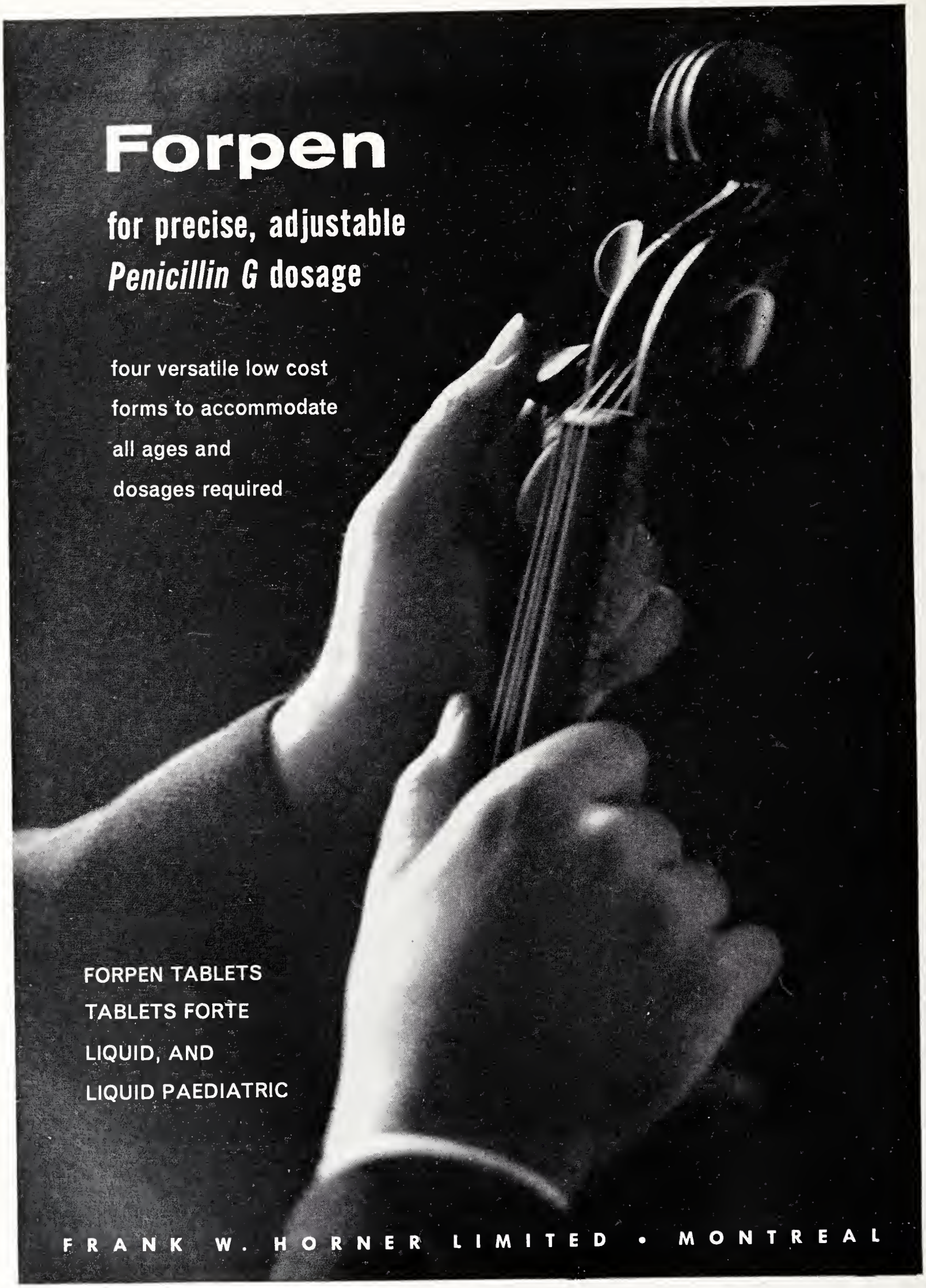

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Nerve Cell Regeneration

M. J. Ball 6T3

Axonal reaction, a common denominator in 'medical' as well as 'surgical' nerve lesions, is discussed and partially investigated.

PREVIOUS CONCEPTS

As Florey has stated[1], "Regeneration in the brain is confined to *nerve fibres* and the supporting glial tissue, for everyone agrees that *adult nerve cells cannot divide,* except in certain tumors."[1] Before dealing with experimental investigation of cellular morphology during nerve cell regeneration, a brief review of the previous concepts of nerve cell and nerve fibre regeneration is essential.

When a peripheral nerve fibre is severed[2], the peripheral portion, cut off from its nerve cells, soon shows fragmentation of its axons and degeneration of the investing myelin sheaths. Before regenerating sprouts from the central portion can grow along the old pathways, Schwann cells from both degenerating stumps must migrate into the space between the cut ends, and there must be active proliferation of fibroblasts from surrounding connective tissue to provide further support for regenerating axons.

Concomitantly, the central stump undergoes similar destruction, back to the next node of Ranvier. Two days after section, new axon sprouts begin to extend distally among the Schwann cells (at a rate of about one millimetre per day); after one week they become enclosed in myelin. *Control of this regeneration is a function of the involved nerve cells themselves.*

The cell-bodies of such severed fibres manifest a particular histologic appearance, known as *"axonal reaction"*. This phenomenon accompanies not only experimental and traumatic injuries, but also such pathologic lesions as occur in vitamin deficiencies, limb amputations, spinal cord tumors compressing nerve roots, and severe peripheral neuropathies (e.g. diabetes, porphyria, Guillain-Barré syndrome).

Axonal Reaction

The most prominent morphologic features of this phenomenon are[3]:

1. *"central chromatolysis"* — disappearance of the Nissl substance, in which the granules vanish first at the centre of the cell;
2. considerable increase in the size of the cell;
3. displacement of the nucleus toward the cell periphery.

The earliest changes of this "dissolution" phase appear 40 hours after section, and are maximal by 15 to 20 days. A phase of "reformation" then commences, progressing more slowly until the cell appears normal once more. A small percentage of affected cells never recover, but go on to die.

The *pathophysiology* of axonal reaction is to date largely unexplained, and three problems still to be solved are now considered.

1. Most investigators accept that the nearer the site of section to the cell-body, the more pronounced is the cell's axonal reaction. No adequate explanation for the cause of this relationship has been advanced.

2. Various workers suggest that the duration and degree of chromatolysis[3], as well as the nucleus' behavior[4], depend on the *type* or *nature* of injury to the axon. "If the nerve be torn out, the reaction is more severe . . . than that which follows section, ligature or pressure of the nerve."[3] Again, no satisfactory explanation of this phenomenon has been forthcoming.

3. Parker has postulated[4] that the neurofibrils* are instrumental in the "antidromic conduction of a chemical change which initiates axonal reaction". Yet the nature of such a change, and the method of its conduction centrally, remain conjecture.

Previous Hypotheses

Consideration of some of the previously advanced theories may help to answer the problems mentioned.

Protein Synthesis. Several workers have concluded that chromatolysis is a reflection of *stepped-up protein production.* In the investigation[5] of the rate of incorporation of free amino-acids into ganglion cell proteins during regeneration of peripheral nerve processes, histologic localization with autoradiographs has shown a marked increase in the concentration of labelled amino-

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* Neurofibrils — fine, thread-like structures forming a network in the body of a nerve cell, and extending into the dendrites.

acids in the perikarya of affected cells. This was interpreted as indicating that regeneration of peripheral processes is accompanied by a vigorous increase in protein synthesis in the cell-bodies.

Barr and Bertram[6] have observed that about 48 hours after traumatizing the cat's twelfth cranial nerve, the nucleoli of affected cells increase in size and exhibit much more vacuolation. This observation is consistent with the view that the nucleolus, containing ribonucleic acid (RNA), is important in the synthesis of ribose nucleoprotein, a prime constituent of Nissl substance.

In addition, Einarson[7] found that, particularly after *severe* axon injury, chromophil material can be seen migrating from the nucleolus, through the nuclear membrane, and then as Nissl substance in the cytoplasm. He therefore suggested that Nissl substance is a product of nuclear activity formed in adult nerve cells by diffusion from the nucleus — *nuclear reparation*. During axonal reaction its formation might be accelerated for repair purposes.

Protein Transport. It seems likely that the *utilization* of new protein material would occur at the site of injury, rather than in the perikaryon; this suggests movement of the protein to the site of injury. If the "new" proteins synthesized in the cell-body move along the axon, it should be possible to collect them at the regenerating end of the fibre. Hence Miani[8] prepared tissue samples for radioactive determination from the growing segments of rabbits' nerves crushed by cooled forceps (—70° C.), after tagged amino-acids had been introduced near the appropriate cranial nucleus. The significant radioactivity after 40 hours (identified by paper chromatography as those amino-acids used) was explained on the basis of a *proximo-distal movement* of protein from the cell-body. The invasion of the axon hillock by Nissl substance[7] is also compatible with this explanation.

Gradients. Investigations suggest that a gradient of certain materials exists in the axon. A study of the distribution of cholinesterase throughout the unbranched trunk of the phrenic nerve after section[9] revealed that there is a *proximo-distal gradient* of enzyme concentration, the activity of the most proximal part exceeding by some 20% that of the distal. Lubinska[10] postulates a similar proximo-distal gradient for "substances relevant to the maintenance of myelin". It is possible that such a gradient might apply to *most* chemical constituents of the axon.

Flow of Axoplasm. A continual proximo-distal movement of protoplasm has frequently been postulated to account for both experimental and clinical observations. This concept would, for example, explain Sunderland's finding[11] that the regenerative rate in all segments of human peripheral nerves appears to be faster after *axonotmesis* (by crushing) than after *neurotmesis* (by cutting and suturing).

After suture, more scar tissue forms at the site of union[12]. In addition, throttling of the cell-body's contributions is said to bring a corresponding reduction in growth[13]. The greater cicatrization would certainly constrict the axons passing through, and might represent this throttling. Weiss[14] believes, in fact, that the phenomenon of *damming of axoplasm* proximal to a constricted nerve is a sign of perpetual growth in nerve fibres . . . i.e., a piling-up of growing axon-substance pressing distally.

If Weiss' idea is valid, the more scar tissue and consequent constricting effect, the more "axon-damming", and therefore the slower the rate of growth possible peripherally, if "building materials" are in fact conveyed from the cell-body by this translatory movement of axoplasm.

A Workable Theory

The various ideas discussed above suggest a plausible solution to the three basic problems already outlined. Let us suppose that the productive processes of the cell-body depend upon the concentration of protein, enzyme, or other material in the proximal area of the axon. Assume, for example, that by the Law of Mass Action, *the rate of production of axoplasm varies inversely as the concentration of ribonucleoprotein in the axon hillock.*

Thus, in cutting the axon, a small leakage of protoplasm causes a decrease in this concentration, in turn stimulating the perikaryon to increase its growth functions, and the picture of axonal reaction results. The notion that chromatolysis represents *hyper*-activity rather than degeneration is well supported by several studies; for example, Hartmann[15] recently found increased numbers of perikaryal mitochondria soon after axonal section.

Due to the proximo-distal gradient of neural constituents, the closer the section to the cell-body, the more material leaks out, the greater the production of axoplasm, and the greater the degree of resultant chromatolysis, as Wohlfahrt[16] observed. This gradient could also explain Sunderland's observation[11] that the rate of advance of motor axon tips decreases progressively throughout the recovery period. One may assume that as the nerve grows peripherally, the deficit of protein and thus the "stimulus" to repair, diminish — by replenishment of the missing material (probably by the nucleus).

Discussion

It seems reasonable to assume that as the growing neuron increases its production of protein, it must reflexly *de*crease its "output" of conduction enzymes, i.e., of the Acetylcholine system. That such a correlation might exist betwcen "synthesizing" activity and "impulse-transmitting" processes can be deduced from the work of Bodian and Mellors[17], who vaguely hint at what might be called an "*Energy Equilibrium*".

The *early* period of axonal rcaction, in which profuse branching of axons corresponds to degradation of Nissl substance, may be interpreted as a shift of the balanced steady state of normal Nissl material in favor of degradation. This results from the increased requirements for protein, occassioned by and probably occurring at the vigorously regenerating sprouts.

In other words, the upsetting of the "Energy Equilibrium" in axonal reaction favors rebuilding functions at the expense of transmission activities. The upset would certainly explain the observations of Chako and Cerf[18], who after sectioning ventral roots, found that the corresponding motor nuclei showed a marked decrease in cholinesterase content.

On the other hand, the recovery period, corresponding to the *gradual* lengthening of the axon, can be regarded as a gradual restoration of the "Energy Equilibrium" — especially because the now lengthened axon may resume utilization of these enzymes of conduction.

Ultrastructural Changes

A final query to be answered is, "Why should increased production of axoplasm be reflected by chromatolysis — i.e., by disappearance of thc Nissl substance?"

One should first realize that "Nissl granules" are revealed by the electron microscope[19] to have two separate components:

1. a layering of three-dimensional reticular sheets, which is part of the general *endoplasmic reticulum* of the cytoplasm, but is more condensed in those areas which under the light microscope comprise the Nissl bodies;

2. small granules (of ribonucleoprotein) disposed either in close contact with the outer membranes of the reticulum or scattered in the intervening matrix (in patterned arrays, e.g., rosettes).

An increased synthesis of axoplasm might involve three simultaneous processes: increased depolymerization of ribonucleotides,[20] increased distal transport of the resultant constituents to the site of regrowth, and increased formation of axon materials at thc lesion, perhaps by repolymerization.

The first of these would likely necessitate separation of the small granules from the reticulum and from each other, thus making the Nissl material less visiblc at light-microscope magnification. The second phenomcnon would add to that effect.

EXPERIMENTATION

Despite extensive investigation of axonal reaction and regeneration of peripheral nerves for more than half a century, certain basic conclusions still lack well-controlled experimental confirmation. To this group belongs the statement that the severity of axonal reaction depends on the type of peripherally applied axonal injury. Definite and convincing experimental proof to substantiate this widely held viewpoint has not been presented.

In order to investigate the effect of the *type* of nerve injury on axonal reaction, three types of lesions have been produced in exactly the same position relative to the cell-body, and in the same species. In addition it was decidcd to rcpeat the experiment of Nicholson[21], who observed disappearance of nerve cells in the rat's hypoglossal nucleus after avulsion of the twelfth Cranial nerve in the neck. This rapid and severe reaction of neurons may be peculiar to the species, or may bc due to thc proximity of the avulsive lesion to the cell-body.

Method and Materials. The four proccdures selected were: *cutting* (the peripheral nerve was sectioned, and a piece about one centimetre long removed; or thc ventral rootlets of a spinal cord scgment were cut); *freezing* (by applying a chip of dry (CO_2) ice to the nerve or ventral root for ten seconds); *ligation* (by tying a silk suture thread tightly around the nerve or all the rootlets); and *evulsion* (by pulling on the hypoglossal nerve with forceps until the nerve snapped at the hypoglossal foramen).

Adult animals of both sexes included guinea pigs, in which the sciatic nerve was cut or frozen; rats, in which the hypoglossal nerve was evulsed, cut or frozen; and cats, in which the anterior (motor) root of L_6 was cut, frozen, or tied. Following survival times of from five to 131 days, material was taken for light microscope examination. This included the lumbar portion of the spinal cords, the medulla oblongata, and the ventral rootlets, as well as affected portions of nerve.

Observations. The data available to date was analysed.

1. Section of a nerve causes degeneration of its peripheral part and the formation of a neuroma at the end of its central stump.

2. Freezing produces relatively little trauma to the nerve, and many of its fibres soon bridge the lesion.
3. Following ligation, some of the regenerating axons grow around the *outside* of the "ring" of silk thread and thus bypass the constricted area.
4. Evulsion of the twelfth Cranial nerve does, in fact, produce complete loss of cells in the hypoglossal nucleus of the brainstem (within about 30 days).

An attempt was then made to classify the *degree* of chromatolysis in the ventral horn of the lumbar cords, before knowing the type of injury which corresponded to the slides being examined. So far, the results of this comparison are inconclusive.

Conclusion. The observations indicate that differences in cellular response to various axonal lesions, if they exist at all, are very slight. It is possible, however, that the conventional methods of evaluating axonal reaction by inspection of histologic sections is too subjective and not sufficiently accurate, and that a more quantitative approach may prove necessary. Definitive statements on the matter must await completion of the current project.

ACKNOWLEDGEMENTS

The author respectfully wishes to thank Professor J. Olszewski, Division of Neuropathology, Department of Pathology, University of Toronto, to whom he is indebted for his sincere interest, his energetic guidance, and above all his infinite patience. The kind assistance of Dr. H. Wisniewski, visiting research fellow of the Polish Academy of Science, Warsaw, and of Dr. R. Elgie, assistant resident, Department of Neuropathology, Banting Institute, Toronto, is also acknowledged.

This study was supported by a Summer Fellowship grant for undergraduate medical research from the Muscular Dystrophy Association of Canada.

REFERENCES

1. Sir Howard Florey, *General Pathology* p. 509, Saunders (3rd ed.), 1962.
2. ibid, p. 508.
3. W. Penfield, *Brain* 43:290, 1920.
4. M. Barr & J. Hamilton, *Journal of Comparative Neurology* 89:93, 1948.
5. N. Miani et al, *Journal of Neurochemistry* 7:#3, p. 161, 1961.
6. M. Barr & E. Bertram, *Journal of Anatomy* 85: 171, 1951.
7. L. Einarson, *American Journal of Anatomy* 53:141, 1933.
8. N. Miani, *Nature* 185:541, 1960.
9. L. Lubinska et al, *Nature* 189:122, 1961.
10. L. Lubinska, *Journal of Comparative Neurology* 117:275, 1961.
11. S. Sunderland, *Archives of Neurology & Psychiatry* 56: 133, 1946.
12. S. Sunderland, *Archives of Neurology & Psychiatry* 58: 251, 1947.
13. P. Weiss & A. Taylor, *Proceedings of the Society of Experimental Biology & Medicine* 55:77, 1944.
14. P. Weiss, *Anatomical Record* 88:464, 1944.
15. J. Hartmann, *Anatomical Record* 118:19, 1954.
16. S. Wohlfahrt & T. Sällström, *Comptes Rendus des Séances*, IIIe Congrès Neurologique International, Copenhague, Août, 1939. Rapport 82: pp. 516-526.
17. D. Bodian & C. Mellors, *Journal of Experimental Medicine* 81:469, 1945.
18. L. Chako & J. Cerf, *Journal of Anatomy* 94:74, 1960.
19. S. Palay & G. Palade, *Journal of Biophysical & Biochemical Cytology* 1:69, 1955.
20. J. Gersh & D. Bodian, *Journal of Cellular & Comparative Physiology* 21:253, 1943.
21. F. Nicholson, *Archives of Neurology & Psychiatry* 11: 680, 1924.

VASCULAR CHANGES IN INFLAMMATION

REFERENCES—*Continued from p. 36*

7. Ebert, R. H., Ahern, J. J. and Block, R. G. — Proc. Soc. Exp. Biol. N.Y., Vol. 68, p. 625, 1948.
8. Ebert, R. H. and Barcley W. R. — J. Clin. Investigation, Vol. 29, p. 810, 1950.
9. Ebert, R. H. and Wissler, R. W. — J. Lab. and Clin. Med., Vol. 38, p. 511-522, 1951.
10. Florey, Sir H. — Lectures on General Pathology, W. Saunders and Co. Philadelphia and London. Lecture 3, p. 53, 1954.
11. Germuth, F. G. — J. Exp. Med., Vol. 97, p. 257, 1953.
12. Karush, F., and Eisen, H. N. — Science, Vol. 136, p. 1032, 1962.
13. Mellors, R. C. and Ortega, L. G. — Amer. J. Path., Vol. 32, p. 455, 1956.
14. Menkin, V. — Science, Vol. 123, p. 527, 1956.
15. Moon, V. H. and Tershakovec, G. A. — A.M.A. Archives of Pathology, Vol. 58, p. 255-293, 1954.
16. More, R. H. and McClean, C. R. — Amer. J. Path., Vol. 25, No. 3, p. 413-445, 1949.
17. Movat, H. Z. — Master of Science Thesis (Queen's University) p. 118-126, 1954.
18. Movat, H. Z., More, R. H. and Wolochow, D. — Amer. Jour. Clin. Path., Vol. 35, No. 2, p. 97-104, 1961.
19. Sandison, J. C. — Anat. Rec., Vol. 50, p. 355, 1930.
20. Sandison, J. C. — Anat. Rec., Vol. 28, p. 281, 1924.
21. Stehbens, W. E. and Florey, H. W. — Quarterly Jour. of Exp. Physiology, Vol. XLV, p. 252-264, 1960.
22. Steiner, J. W., Baumal, R., Movat, H. Z. and McGregor — (Unpublished paper) Dept. of Path., University of Toronto, 1961.
23. Steiner, J. — Amer. J. Path., Vol. 38, p. 411-436, 1961.
24. Steiner, J. W., Slater, R. J. and Movat, H. Z. — Lab. Investigations, Vol. 102, 1961.
25. Tokuda, S. and Weiser, R. C. — Science, Vol. 127, p. 1237, 1958.
26. Trapani, I. L., Garvey, J. S., Campbell, D. H. — Science, Vol. 127, p. 700, 1958.
27. Waugh, D., and More, R. H. — Amer. J. Path., Vol. 27, p. 758, 1951.
28. Weiser, W. J. — Description of the Rabbit Ear Chamber (with certain modifications) (Unpublished paper).
29. Zeek, P. M. — New Eng. Jour. of Med., Vol. 248, p. 764-772, 1952.

Answers to On Inspection

FIGURE 1. Pituitary Dwarfism (Lorain-Levy Syndrome).

This rare condition of obscure etiology is thought to be due to a reduction of growth hormone, and is usually associated with a suprasellar cyst or craniopharyngioma. In most cases there is evidence of reduction of other anterior pituitary hormones as well. The outstanding clinical characteristics are symmetrical impairment of growth occurring only after the first year, normal body proportions, and subnormal sexual development.

CLASSIFICATION OF DWARFISM:

A. *General Decrease in Stature:*

1. Primordial Dwarfism: small at birth with slow rate of skeletal growth, but otherwise normal.
2. Cachexia: due to a chronic wasting disease.
3. Osteogenesis Imperfecta: multiple fractures and blue sclerae.
4. Diaphyseal Aclasis: bony exostoses.
5. Osteopetrosis: increased bony sclerosis.
6. Progeria: premature senility.
7. Congenital Syphilis: saddle-nose, interstitial keratitis, etc.
8. Macrogenitosomia Praecox: precocious sexual development associated with a tumour of the pineal body.
9. Adrenogenital Syndrome.
10. Ovarian Agenesis: (See Below).
11. Burnier's Syndrome: associated with optic atrophy and due to a tumour pressing on the pituitary.
12. Laurence-Moon-Biedl Syndrome: obesity, hypogenitalism, mental retardation, and retinal pigmentation.

B. *Short-Limb Type*:

1. Achondroplasia: commonest form of dwarfism; large heads, short trident hands, protruding buttocks, with somewhat short but normal appearing trunk.
2. Cretinism: puffy eyelids, protruding tongue, depressed nasal bridge, etc.
3. Osteogenesis Imperfecta.
4. Epiphyseal Dysplasias: irregularity in density of developing epiphyses and stubby digits.
5. Pituitary Dwarfism.
6. Fröhlich's Syndrome: obesity and sexual infantilism.
7. Rickets: delayed closing of anterior fontanelle, genu varus, etc.

C. *Short-Trunk Type*:

1. Chondrosteodystrophy: marked kyphosis, enlargement of acetabulae, and coxa vara.
2. Gargoylism (Hurler's Syndrome): large head, ugly face, kyphosis, hepatosplenomegaly.
3. Tuberculosis of Spine: severe kyphosis.
4. Severe Scoliosis.

FIGURE 2: Adrenal Carcinoma with Facial Hirsutism

Androgens, or male sex hormones, are found in both men and women, and are secreted, for the most part, from the adrenal cortex, and the testis. Urinary 17-ketosteroids are degradation products of the androgens, although some androgens are not metabolized to 17-ketrosteroids, and indicate generally the level of androgen production by the body. Increased levels of circulating androgens in the female, indicated by an elevated level of 17-ketosteroid excretion, are an important cause of virilism, including facial hirsuitism. The very high levels of 17-ketosteroid excretion (eg. 800 mg/24 hrs.) are seen principally in adrenal hyperplasia and adrenal tumours; to differentiate the two one could carry out an ACTH stimulation test and a dexamethasone suppression test. Other less common causes of increased androgen production in the female with facial hirsutism, are the arrhenoblastoma, and hilar cell tumour of the ovary, and the Stein-Leventhal Syndrome. Facial hirsutism is also an important feature of Cushing's Syndrome, and overadministration of androgens. However, the majority of women who seek advice for facial hirsutes have no gross endocrine disturbance and their only trouble is that they chose hairy parents or parents with hairy brothers and sisters.

FIGURE 3: Hypertrophic Osteoarthropathy (Clubbing of the Fingers)

This disorder is characterized by clubbing of fingers and toes, chronic periostitis with new bone formation, and arthritis. Many theories have been advanced to explain the pathogenesis of this condition, but the issue is still in doubt. The conditions with which symmetrical clubbing is associated are:

A. *Acquired*:

1. Pulmonary: carcinoma, abscess, empyema.
2. Cardiac: Subacute bacterial endocarditis, cyanotic congenital heart disease.
3. Hepatic: cirrhosis, especially biliary.
4. Gastrointestinal: ulcerative colitis, regional enteritis, polyposis, neoplasms.
5. Miscellaneous: after thyroidectomy for Graves' disease, spontaneous myxedema, syringomyelia.

B. *Idiopathic.*

C. *Hereditary.* (No arthritis).

Unilateral clubbing is most commonly caused by aneurysm of aorta, innominate or subclavian. Other causes are apical lung cancers, axillary tumours, brachial arteriovenous anastomoses.

Unidigital clubbing is sometimes found in cases of hyperparathyroidism, and is probably due to resorption of the terminal phalanges.

FIGURE 4: Syndrome of Gonadal Dysgenesis

The features of the syndrome of gonadal dysgenesis are rudimentary gonads, female genital ducts and external genitalia, sexual infantilism after the age of adolescence, and a physical appearance characterized by an underdeveloped mandible, high arched palate, broad chest, widely spaced and hypoplastic nipples, cubitus valgus, short neck which is often webbed, low hairline posteriorly, and an increased number of pigmented nevi and telangiectases of the skin.

The syndrome of gonadal dysgenesis may be due to:

1. Gonadal Aplasia (Turner's Syndrome): The gonad is reprcsented only by an unidentifiable fibrous streak in the broad ligament. Most have an Xo chromosomal pattern.
2. Gonadal Dysgenesis with Medullary Elements: Rete tubules, and Leydig cells are present in the genital streak. The chromosomal pattern is Xo or Xy.
3. Gonadal Dysgenesis with Corticel Elements: Presence of primordial follicles in cortical component of primitive gonad. Chromosomal pattern is Xo or XX. When edema is present, usually in face and extremities, the condition is called the Bonnevie-Ulrich Syndrome.

FIGURE 5: Pretibial Myxedema in Hyperthyroidism.

This condition, also called localized myxedema, which is essentially a swelling of the skin and underlying subcutaneous tissue is observed occasionally in patients who either have, have had, or probably will have thyrotoxicosis. The lesions are frequently bilaterial and symmetrically placed. The skin has a brownish induration, and a large quantity of mucinous-staining material is deposited between the collagen bundles. The cause is thought to be due to a localized deficiency in thyroid hormone action.

FIGURE 6: Pigmentation of Tongue in Addison's Disease.

Addison's Disease or chronic Primary Adrenocortical Insufficiency is due to bilateral tuberculosis (50%), primary atrophy (46%), amyloid disease (2%), neoplasms (1%), and other rare causes. Hyperpigmentation is a classical clinical feature of Addison's disease and represents an increase in the deposition of melanin in the skin and mucous membranes.

Adrenocotrical insufficiency results in an increased production of ACTH by the anterior pituitary gland. ACTH has stimulating effect on melanocytes which is qualitatively similar to but only 1/100 as potent as that of the melanocyte-stimulating hormone (MSH), which is elaborated in the pars intermedia of the pituitary gland. The structural similarity of ACTH and MSH explains the overlapping actions of these otherwise unrelated pituitary peptides. Hence it has been postulated that the high level of circulating ACTH, rather than that of MSH, about whose biologic significance little is known, is responsible for the hyperpigmentation of Addison's disease.

The differential diagnosis of a slate-gray to brownish hyperpigmentation must include racial and idiopathic pigmentation, hemochromatosis, regional enteritis, ulcerative colitis, hepatic cirrhosis, Peutz-Jegher's syndrome, melanoscarcoma, acanthosis nigricans, neurofibromatosis, polyostotic fibrous dysplasia (Albright's Syndrome), skin irritation, nutritional deficiencies, pernicious anemia, scleroderma, and dermatomyositis.

FIGURE 7: Metabolic Metastatic Calcinosis Due to Hypervitaminosis D.

The most common cause of hypoparathyroidism is damage to, or removal of, the parathyroid glands in the course of an operation on the thyroid gland. There is a resultant decrease in renal tubular secretion of phosphate by the kidneys, resulting in an elevation of the plasma phosphate concentration; this leads to an increase in the ion product of calcium and phosphate in the plasma and to an increase in the deposition of these ions in bone. This is followed by a fall in plasma calcium concentration. Other factors contributing to hypocalcemia arc, decrease in absorption of calcium from the gastro-intestinal tract, and the decrease in rate of bone resorption.

The major objective in the treatment of this disease is to elevate the plasma calcium concentration to a normal range; the most important single agent for this purpose is Vitamin D; also important are a high-calcium low phosphate intake.

In patients who have received excessive amounts of Vitamin D (150,000 units per day or more), there may be produced the syndrome of Vitamin D intoxication (hypervitaminosis D), consisting of hypercalcemia with hyperphosphatemia, impaired renal function, polyuria and polydispsia, anorexia, lethargy and constipation. Because of the increased plasma levels of calcium and phosphorus, precipitation of calcium phosphate occurs in abnormal sites (metastatic calcification), including the skin, stomach, lungs and blood vessels. The formation of renal stones predisposes the patient to chronic urinary infection (pyelonephritis).

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The authors wish to thank the following for their assistance: Dr. K. J. R. Wightman, Dr. J. Laidlaw and Mr. A. Smialowski.

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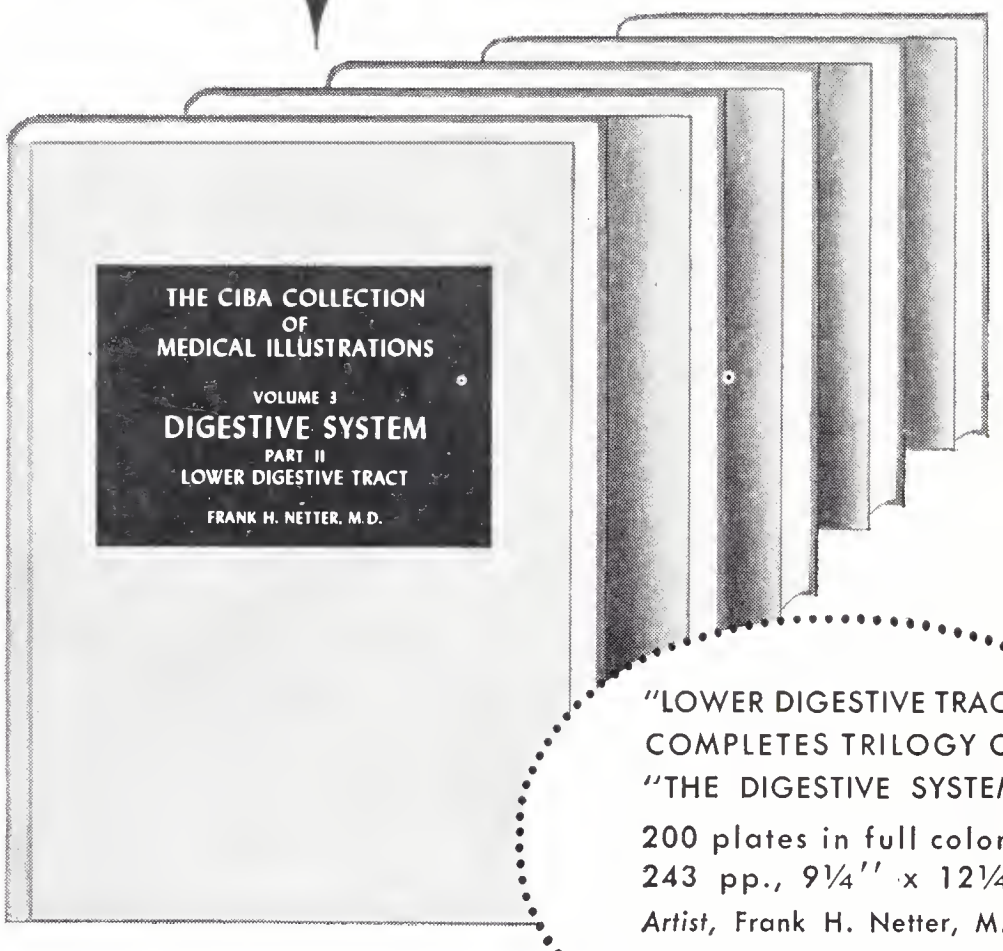

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